Universidade de Aveiro
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Secção Autónoma de Ciências da Saúde

JOANA PEREIRA OLIVEIRA

Relatório de Estágio: Coordenação de Ensaios Clínicos na Perspectiva de uma Clinical Research Organization vs Centro de Investigação

Curricular Training Report: Clinical Trials Coordination in a Clinical Research Organization vs an Investigational Site Perspective

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Relatório de estágio apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica de Dra. Maria João Queiroz, global CEO, Eurotrials, Consultores Científicos, Prof. Dr. Nuno Sousa, Presidente da Direção do 2CA-Braga, e do Prof. Dr. Bruno Gago, Professor Auxiliar Convidado da Universidade de Aveiro.

Curricular training report to be presented to the University of Aveiro to complete the necessary requirements for the Masters' Degree in Pharmaceutical Medicine, held under the scientific guidance of Maria João Queiroz (MD), Global CEO of Eurotrials, Scientific Consultants; Nuno Sousa (MD, PhD), President of 2CA-Braga Direction; and Bruno Gago (PharmD, PhD), Invited Assistant Professor at University of Aveiro.

I dedicate this work to my parents, sister and boyfriend for their unconditional support, and to the memory of my grandfather Abílio.

juror

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“All our dreams can come true, if we have the courage to pursue them.”

Walt Disney

palavras-chave

Eurotrials, 2CA-Braga, Ensaios Clínicos, Monitorização de Ensaios Clínicos, Coordenação de Ensaios Clínicos, Medicina Farmacêutica, Investigação Clínica, Sistema de Gestão de Qualidade, Acordo Financeiro de Estudos Clínicos

resumo

Este relatório descreve a minha experiência de nove meses enquanto estagiária numa CRO (Eurotrials, Consultores Científicos) e num centro de investigação clínica (Centro Clínico Académico – Braga, Associação).

Este documento começa por analisar o enquadramento europeu da investigação clínica e, posteriormente, a situação portuguesa comparativamente a países similares. De seguida, são descritas as atividades desenvolvidas no âmbito deste estágio, as quais foram divididas em duas fases.

A primeira fase desenrolou-se na Eurotrials, Consultores Científicos, uma CRO especializada em investigação clínica e consultoria científica. As primeiras semanas foram dedicadas ao treino e à formação necessários para o desempenho de tarefas como assistente de estudos clínicos. Estas tarefas incluíram a participação em várias atividades de qualificação, iniciação e monitorização de estudos clínicos, assim como o desenvolvimento e aperfeiçoamento de um sistema de gestão de qualidade.

A segunda vertente decorreu no 2CA-Braga, um centro de investigação clínica localizado no Hospital de Braga. Nesta fase, o estágio focou-se essencialmente na coordenação de estudos clínicos, assim como, em atividades relacionadas com o processo de revisão/negociação de contratos financeiros. Para além disso, tive a oportunidade de participar nas "1as Jornadas de Investigação Clínica e Inovação" organizadas pelo 2CA-Braga.

Globalmente, o estágio traduziu-se numa excelente oportunidade para ganhar conhecimentos e experiência nas tarefas associadas a projetos e serviços no âmbito da implementação e gestão de estudos clínicos, na perspetiva de uma CRO e de um centro de investigação clínica. A integração destas duas perspetivas permitiu-me identificar e confluir necessidades específicas de diferentes *players* envolvidos na investigação clínica.

Concluindo, este estágio permitiu-me aplicar e aperfeiçoar os conhecimentos adquiridos durante a minha formação académica tornando-me capaz de enfrentar e transpor novos desafios na área da investigação clínica.

keywords

Eurotrials, 2CA-Braga, Clinical Trials, Clinical Trials Monitorization, Clinical Trials Coordination, Pharmaceutical Medicine, Clinical Investigation, Quality Management System, Clinical Study Financial Agreements

abstract

This report describes my experience of nine months as a trainee of a CRO (Eurotrials, Scientific Consultants), as well as a trainee of a clinical research site (Clinical Academic Center – Braga, Association).

This document describes the European framework about clinical research and the Portuguese situation compared to similar countries. The activities developed during this internship are also described. These activities are divided in two phases.

The first one occurred in Eurotrials, Scientific Consultants, a CRO specialized in clinical research and scientific advice. The first weeks were dedicated to intensive self-training needed to perform CTA tasks. These tasks included qualification, initiation and monitoring activities related to clinical trials, as well as the development of a quality management system.

The second phase took place on 2CA-Braga, a clinical research center located in Hospital of Braga. Clinical studies coordination was the main focus of this second phase of my internship, as well as negotiation of clinical studies agreements. I had also the opportunity to participate in "1as Jornadas de Investigação Clínica e Inovação" (1st Clinical Investigation and Innovation Conference) organized by 2CA-Braga.

Globally, this internship was a great opportunity to get knowledge and experience in the implementation and management of clinical trials, in a CRO and clinical research site perspectives. These two perspectives provided an interesting overview about the scientific needs of different players involved in clinical research.

To conclude, this internship strengthened the knowledge acquired from my academic background, which make me able to face and overcome new challenges in the clinical research area.

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Abbreviations

AIDS Acquired Immune Deficiency Syndrome

AE Adverse Event

2CA-Braga Clinic Academic Center – Braga

CAT scan Computerized Axial Tomography Scan

CDA Confidentiality Disclosure Agreement

CEIC Central Ethics Committee

CEO Chief Executive Officer

CNPD Data Protection Authority

CRA Clinic Research Assistant

CRF Case Report Form

CRO Clinic Research Organization

CSA Clinic Study Agreement

CT Clinic Trials

CTA Clinic Trials Assistant

CV *Curriculum Vitae*

eCRF Electronic Case Report Form

EFPIA European Federation of Pharmaceutical Industries and Associations

EMA European Medicines Agency

FDA Food and Drug Administration

GCP Good Clinical Practices

GNP Gross National Product

HIV Human Immunodeficiency Virus

ICF Informed Consent Form

ICH International Conference of Harmonization

ICVS Life and Health Sciences Research Institute

IMI Innovative Medicines Initiative

INFARMED National Authority of Medicines and Health Products

IP Investigational Product

ISF Investigational Site File

IVRS Interactive Voice Response System

IWRS Interactive Web-Response System

MRI Magnetic Resonance Imaging

OECD Organisation for Economic Co-Operation and Development

PD Pharmacodynamics

PET Positon Emission Tomography

PI Principal Investigator

PK Pharmacokinetics

POC Proof of Concept

PSV Pre-Study Visit

QMS Quality Management System

R&D Research & Development

SAE Serious Adverse Event

SC Study Coordinator

SDV Source Data Verification

SIV Site Initiation Visit

SOPs Standard Operating Procedures

TMF Trial Master File

UMinho University of Minho

1. Introduction

The present work consists of an internship report developed under the scope of the Master of Science Degree in Pharmaceutical Medicine at Aveiro University. The purpose of this internship was to provide on the job training that would allow contact with different players of R&D environment and to put into practice the concepts and competences acquired in this scientific area during the masters.

This internship lasted for nine months and it was divided in two different phases. The first two months occurred in R&D and Clinical Trials Departments of Eurotrials, Scientific Consultants and the other seven months took place in 2CA – Braga, in its facilities in Hospital of Braga.

This report presents the state of the art and a brief overview of Clinical Research and Development in Europe and Portugal. Then, the objectives of this internship and a description of the host institutions structure and organization are provided. The main projects and activities performed during this nine-month internship are described in Eurotrials and 2CA-Braga Training Activities sections. This report ends with a discussion of the main goals and difficulties from the activities performed during this internship, including an assessment about the achievement of the learning outcomes defined at the beginning of my internship. The value of a study coordinator professional in clinical research is once more stated in the conclusion of this report.

1.2 State of The Art

This section presents an overview of the Pharmaceutical Research and Development (R&D) process in Europe since its beginning, describing a new R&D model for drug development. It also describes the current situation of performing clinical trials in Portugal.

In chapter 2.1, European R&D process is compared with the rest of the world. In chapter 2.2, the evolution of clinical research and clinical trials in Portugal is compared with other similar countries.

1.2.1 Pharmaceutical Research and Development Process in Europe vs Other Regions

Medicine is an art that has been practiced since time immemorial. The use of herbs and natural medicines to relieve pain has been a part of all societies. (1,2)

Until the twentieth century, the sale and use of medicines and medical devices was almost entirely unregulated by governments. Patent Medicines and “sake oils”, products which are promoted and sold as medical cures but does not provide the promised relief, became available in pharmaceutical

market. These situations eventually led to government intervention and professional regulation. It became necessary to demonstrate that drugs were pure and unadulterated before its marketing. With advances in science and in the ability to define and establish drug efficacy came a requirement to demonstrate that drugs were also safe. In the second half of the twentieth century, came the legal requirement to establish that pharmaceuticals are effective before they are marketed. European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the United States are responsible for establishing these rules and to ensure their implementation. (1,2)

The exponential growth in scientific knowledge has brought a paradigm shift in our approach to pharmaceuticals.

This paradigm shift reflected a history of pharmaceutical development filled with multiple successes that resulted in huge economic gains and in valuable innovative medical therapies. A large number of diseases that were classified as life-threatening, in areas like cancer, cardiology and infectiology, are now curable or considered chronic and manageable diseases. Prescription medicines have altered the trajectory of many debilitating diseases, resulting in decrease death rates for a number of conditions, improved health outcomes, and better quality of life. (2,3)

An example is the HIV/AIDS disease. Tremendous strides have been made over the past 25 years in the prevention and treatment of HIV/AIDS. Since peaking in 1995, death rates have fallen exponentially. (figure 1)

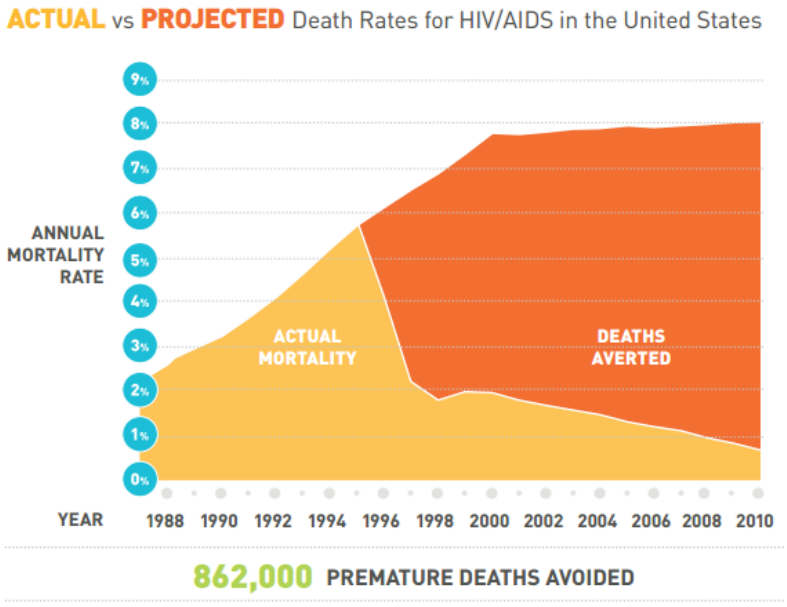


Figure 1: *HIV: decline in Death Rates* (4)

Treatment adherence among patients has improved because of reduced side effects, improved ease of use and reduced pill burden, which has contributed significantly to improving and extending the lives of HIV patients.

Today, 20-year-olds diagnosed with HIV can expect to live into their early 70s - a life expectancy close to that of the general population. A recent study found that since the introduction of combination antiretroviral therapies in the mid-1990s, more than 862,000 premature deaths have been avoided and 27.7 million life years have been gained (figure 1). (3,4)

After this constant growth period, supported by the development of blockbusters drugs that targeted vast population groups, the productivity of European pharmaceutical industry has been declining. (2)

Pharmaceutical companies have been facing real challenges because of the impact of fiscal austerity measures introduced by governments across much of Europe that resulted in pharmaceutical companies R&D spending decline. (5,6)

One of the major reasons for the investment decrease in Europe is the price control of medicines that are not ruled by free competition laws, but fixed by the governments on a national basis. Stricter regulatory approval processes and efforts to contain healthcare expenditures have had a tendency to restrict the growth of markets in Europe. This has resulted in a lucrative parallel trade between countries with significant price differences.

These countries are known by emerging markets. Emerging economies such as Brazil, Russia, India and China (BRIC) have lived a rapid growth in the pharmaceutical market and research environment. In 2011 the Brazilian and Chinese markets grew 20.0% and 21.9% respectively, compared with an average market growth of 2.6% for the five major European markets and 3.6% for the USA market. Europe has been losing competitiveness compared to others regions of the World and it is anticipated that markets in the emerging countries will continue to grow another 14-17% by 2014/2015, compared with 3-6% for developed markets. (5–7)

The investment in R&D has influence in the knowledge obtained and can influence the number of new medical entities.

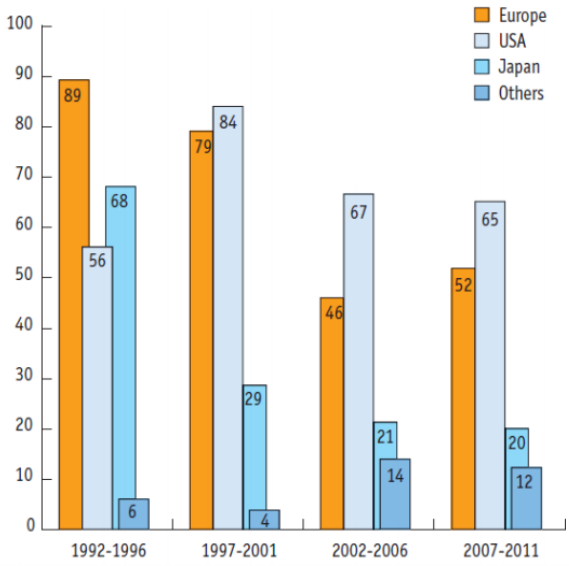


Figure 2: Number of new medical entities, 1992-2011 (7)

Figure 2 highlights how the number of new discoveries has been decreasing in Europe. This reduction occurred even in years where the R&D investment in Europe increased. The R&D investment hasn't been translated into new medicines. This is a problem called Translational Gap and it occurs when a lot of R&D investment results in a lot of scientific information that is not translated in applied knowledge and new products. This Translational Gap could be consequence of a change in the good enough concept. "Ten years ago, if you had a drug that was a little better than or even as good as something already in the market, you could get it approved.

Those days are gone." (Jonathan Knowles, Chairman of the Innovative Medicines Initiative). This concept and also the financial restrictions had as consequence the rejection of the unpromising projects that contributed to the Translational Gap. (2,5–7)

During the blockbusters phase, for a medicine to be adopted and to sell, it was sufficient that science could conceive of a new treatment, which technology could deliver that treatment, and that clinical research could prove its effective and safe use. This is no longer the case. Over the past decades, there are two major influences emerging in decisions about new advances in healthcare: the payer-providers and the patient-consumers. The pharmaceutical medicine of today involves medical sciences to evaluate disease; economic sciences to evaluate the value with respect to costs; and ethical and social sciences to evaluate the utility of any new drug to patients and society as a whole. (2,5,6)

To address these requirements, a deep knowledge about the market and the inherent unmet medical need is needed. There are still medical areas urging for effective treatments. Some kinds of cancer and other medical conditions (as neurological degenerations) have still the need for large

improvements. Those diseases need a more targeted clinical development when compared to the ones traditionally treated with blockbuster's drugs (e.g. cardiovascular). (2,4,6)

The current R&D paradigm is based on a rigid and sequential model including: basic chemical or structural research; pre-clinical research and development; clinical development; regulatory and society development; and post-market approval medical affairs.

The basic chemical or structural research phase aims to explore the genetic basic of a disease or the microstructure of a receptor or enzyme active site, and from that, developing tailored molecules to provide specific interactions and potential therapeutic outcomes.

Pre-clinical research and development use biological systems, up to and including animal models, to explore the causes of diseases and the potential safety and efficacy of new therapeutic agents.

Clinical development uses humans, both the healthy and those with a disease, to evaluate the safety and efficacy of a new drug. This section is subdivided into three phases: phase I (human pharmacology studies), phase II (therapeutic exploratory studies) and phase III (therapeutic confirmatory studies) clinical trials. In phase I, manufacturers usually test the effects of a new drug in healthy volunteers or patients unresponsive to usual therapies. They look at how the drug is handled in the human body (pharmacokinetics and pharmacodynamics), particularly with respect to the immediate short-term safety of higher doses. Clinical trials in phase II explore dose-response curves in patients and what benefits might be seen in a small group of patients with a particular disease. In phase III, a new drug is tested in a controlled ambient in a large patient population against a placebo or standard therapy. This is a key phase, where a drug will either make or break its reputation with respect to safety and efficacy before marketing begins. These concepts will be schematized in "Clinical Trials Training Activities" section (1,2,8–10)

Regulatory and societal development ensures that the entire development of each new therapeutic product is seen in the context of its need to meet governmental requirements and that the appropriate value-added components (e.g. quality of life, cost-benefit, evidence-based medicine, relative competitive positioning over and above the basic demonstration of safety and efficacy) are integrated into the product's database. (2,9)

Post-Market approval medical affairs include phase IV clinical trials or postmarketing studies (therapeutic use studies) as the drug has already been granted regulatory approval/license. These studies are crucial for gathering additional safety and efficacy information from a larger group of patients in normal clinical practice, as opposed to clinical trials, in order to understand the long-term safety of the drug and appreciate drug interactions. The development of new or improved uses of the product is also assessed in these studies. (1,2,8–10)

The whole process of developing a new drug is extremely expensive and time-consuming. It is also a very difficult and risky process. From the synthesis of a new active substance to marketing approval, an average of twelve (12) to thirteen (13) years will have elapsed. Of every 10,000 substances, only one (1) or two (2) will successfully be marketable medicines. (2,4,6)

One of the most commonly mentioned development problem is the attrition rate of developing new medicines. The large number of unsuccessful drug candidates is also a barrier to investment in innovative, higher risk drugs. However, it has to be fully understood before drafting abrupt conclusions. If the failure of the candidates is related to the research methodology (as in high-throughput techniques) and it has little impact in the overall costs, it does not constitute a major problem. The main issue arises when the candidate fails in later developments phases (phase II or III) when a large number of resources were already spent. The investment in clinical trials conduct represents two-thirds of the cost of developing a new drug (figure 3).

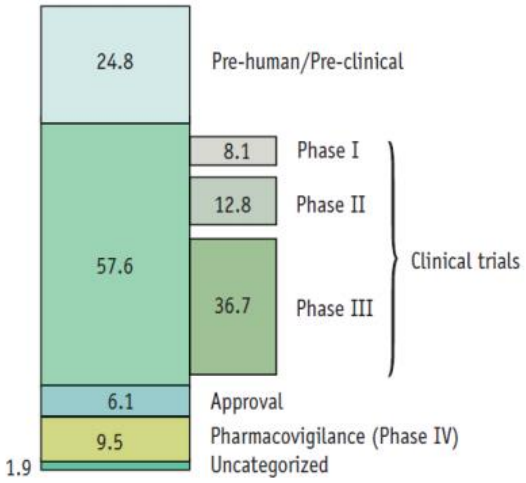


Figure 3: Allocation of R&D investments (%) (11)

The actual rigid and sequential paradigm (phase I to IV) is exceedingly vulnerable to the unforeseen effects of late failures. Indeed, the majority of initial new product leads never reach the level of being tested on humans, and over 88% of the products that are tested on humans never become licensed drugs (figure 4). (2,4,6,8)

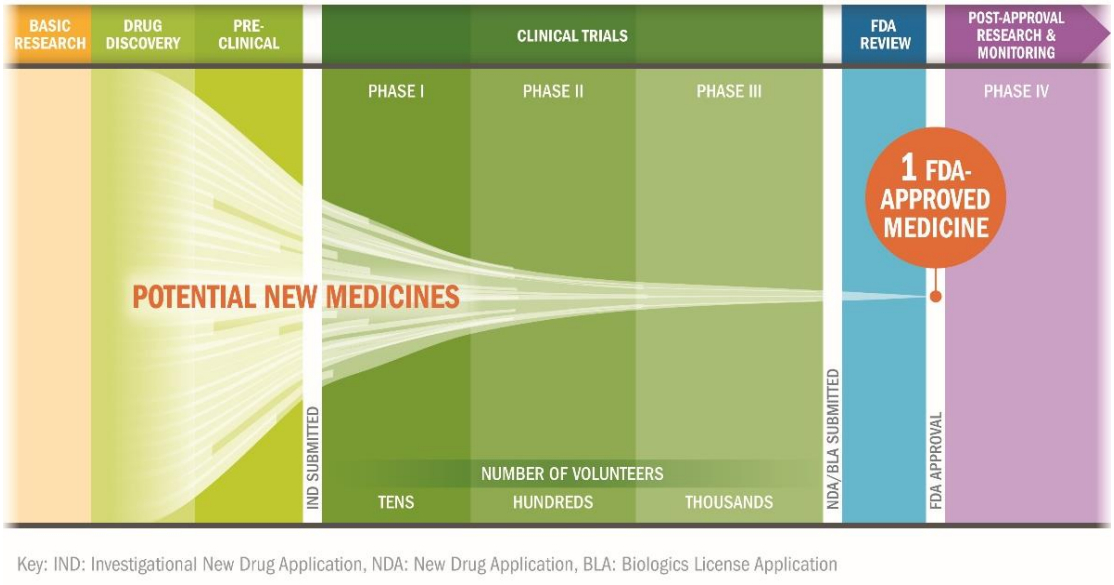


Figure 4: The Actual Biopharmaceutical Research and Development Process (4)

Of course, all of the many failed research and development efforts must be paid for, as well as the relatively few successful projects.

So, a shift from a discovery phase based on high-throughput techniques to a personalized medicine with use of genomics and bioinformatics tools is required.

Faced with an increasingly competitive market and an urgency to reduce costs and difficulties of medical product development, the actual R&D model has to be changed to a more flexible process, based on data: the quick-win fast-fail model (figure 5). (4,6,11,12)

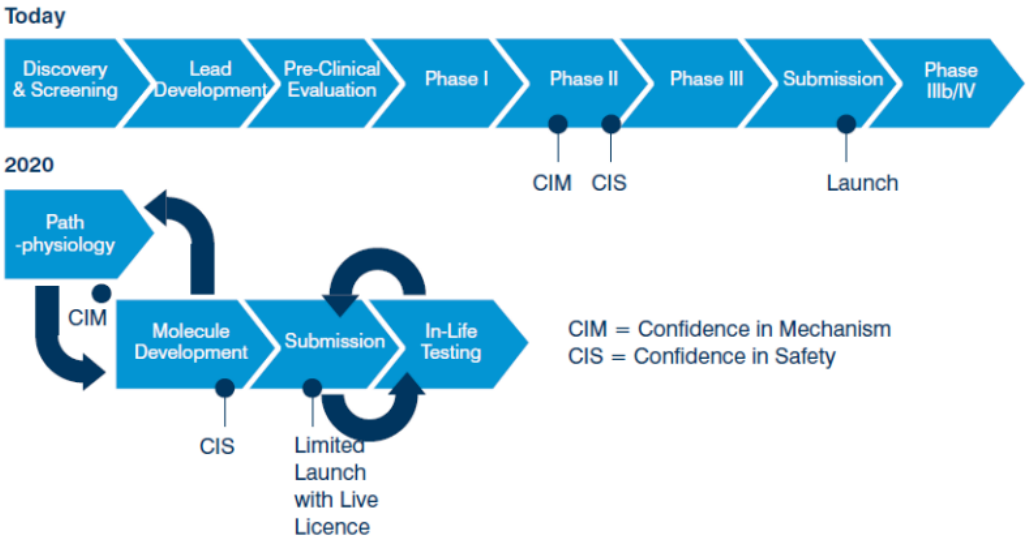


Figure 5: Drug Development Process - current and expected for the future (4)

The quick-win fast-fail model increases the number of final winning products by failing more drug candidates in the early development phases. Establishing the proof-of-concept (POC) before phase

II and the use of an adaptive smooth phase II and phase III are the main principles of this model. More intense early phases will allow to better filter the “bad bets” and to invest the productivity gains in further product development (improved efficacy and new indications).

This model stresses the necessity for a faster test in humans (reducing the inconclusive animal tests and replacing it by emerging in-vitro and bioinformatics tools) and an early safety and efficacy proof. A radical change in the approval process is however proposed: instead of a long and rigid process, the suggested approval is phased and conditioned to a well determined population range and indication (“live licence”). The conditional marketing approval is, if the respective evidence is generated (“life-testing”), gradually expanded with new indications and patient groups. The overall process is based on a strong pharmacovigilance control. (11,12)

To be able to provide an early POC it is necessary to adopt new methodologies of evaluating safety and efficacy. The development of new biomarkers (ideally endpoints surrogates) and the use of new molecular, genomic and imaging technologies are crucial for the practical application of the new paradigm.

Regulators are aware of this paradigm shift and are inclusively making efforts to promote and implement it. The FDA’s critical path initiative in 2004 and the public-private partnership between EU and EFPIA, named Innovative Medicines Initiative in 2008 (figure 6) are some examples. Those initiatives describe specific areas where the sciences of product development had the greatest need for improvement to enhance the accuracy of tests that predict the safety and efficacy of potential medical products. Biomarkers, genomics, imaging, informatics in medicine (the analysis of biological information using computers and statistical techniques), and specific education and training programs are some examples of these areas. (13,14)

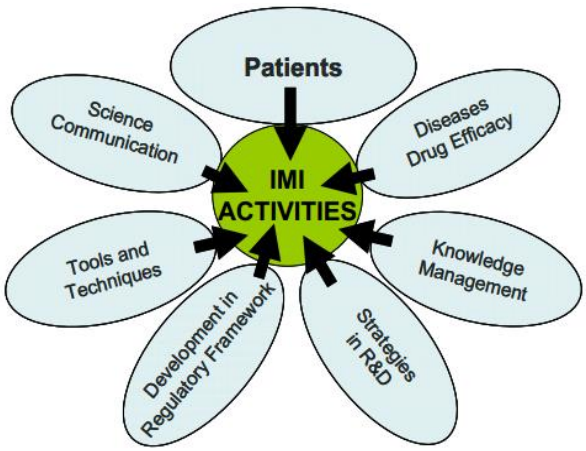


Figure 6: Areas of Research Interest of IMI (13)

Rising costs and increasing budget pressures have started to affect clinical trials forcing companies to rethink how to perform these activities. The choice of the country that best suits the clinical trial

is an increasing concern of the pharmaceutical companies. Depending on the location, cost saving can range from 30% to 65% in emerging markets compared with sites in the United States of America (USA) or Western Europe (WE). In these countries the time to complete clinical trials phases is shorter, which provides earlier relief to patients, a faster return on investment, a potential edge over competitors and a longer patent protection. (7,15,16)

In 2006, the country attractiveness index for clinical trials was developed based on patient availability, cost efficiency, relevant expertise, regulatory conditions and national infrastructures. USA, China and India were considered the most attractive locations (figure 7). (15,16)

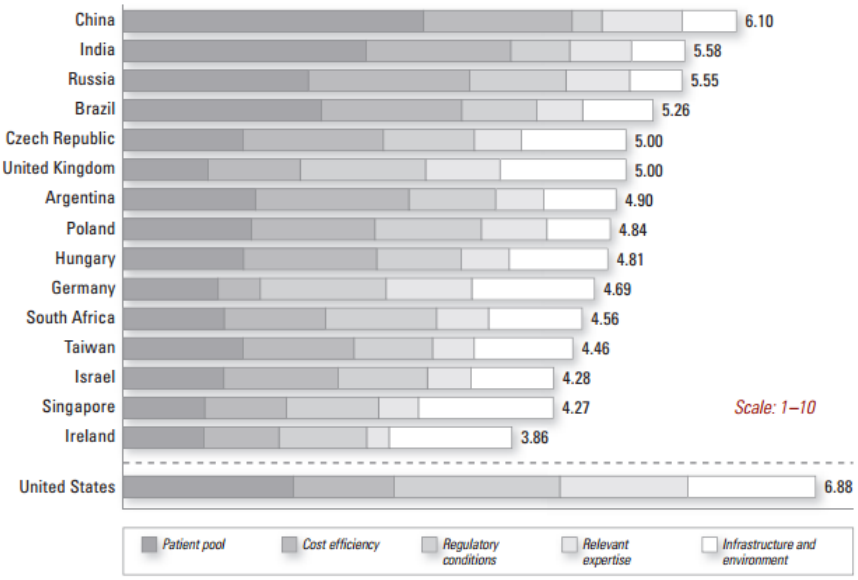


Figure 7: Overall country attractiveness index for Clinical Research (15)

For China to be on the top of this ranking (after USA), several factors were taken into account: the vast patient pool and large infrastructure of the hospitals, the large number of health professionals and their low salaries. India comes in second because it offers vast population, English as primary language, and a growing market and the incentive to promote local pharmaceutical companies and attract foreign firms. Emerging countries are attracting clinical trials due to low costs and the availability of a skilled R&D workforce and large patient population. However, there are many risks in low-cost countries that companies have to consider and that make pharmaceuticals think before choosing one of these countries. They have to: protect intellectual property, know the regulatory requirements and learn the ethnicity and understand cultural differences (that varies widely from country to country). Europe has a vast experience in conducting clinical trials, which means that Europe has a great potential for market growth if the critical obstacles mentioned before are overcome. (4,15,16)

1.2.2 Clinical Trials in Portugal vs Other European Countries

As other European countries, in the last 30 years Portugal has accomplished great achievements in health indicators. Portugal has one of the lowest infant mortality rate (3.6% in 2009) and the highest average annual rate of decline between 1970 and 2009 (6.8%). Between 1960 and 2009, Portugal was able to increase life expectancy at birth by 15.6 years, more than OECD average and any other EU 27 country, reaching an average life expectancy of 79.5 years in 2009 (figure 8). (17,18)

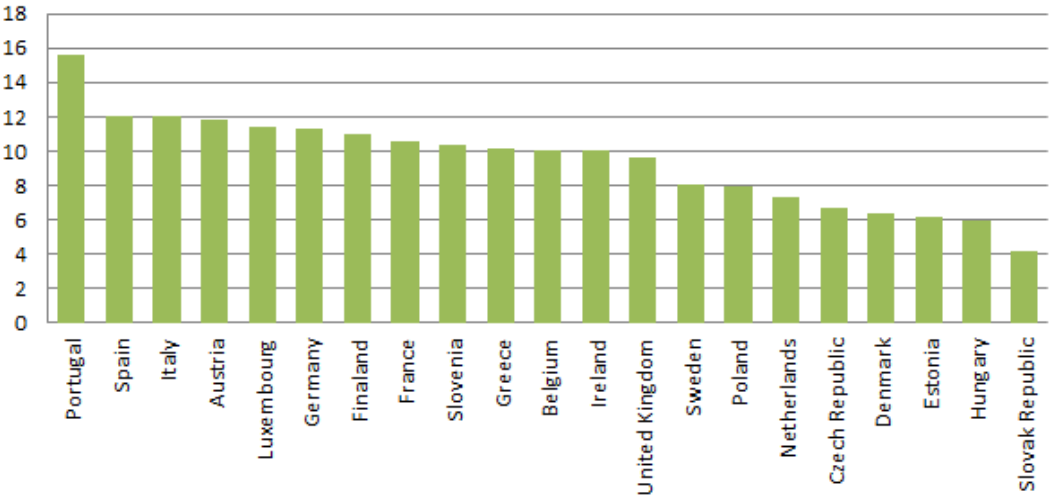


Figure 8: Years gained in life expectancy at birth, 1960-2009 (9)

Medicines have played a very important role in this progress. 40-59% of the increase in life expectancy is due to innovative medicines (figure 9). (5,17,18)

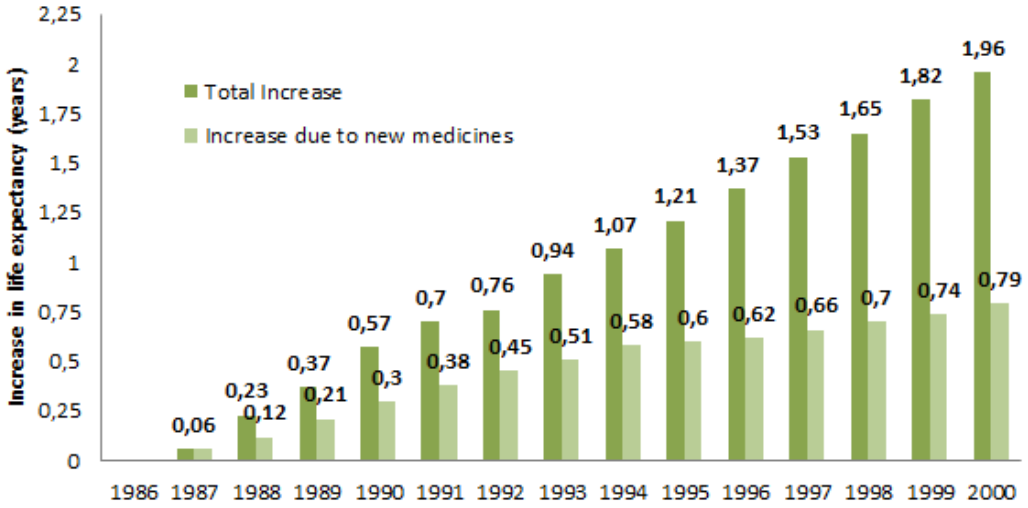


Figure 9: Increase in life expectancy (years) (9)

However, clinical research in Portugal has been losing its leading position on the global investment in Health. By 2012, Europe had a small average market growth of 4%, however Portugal had not

seen any growth and the evolution was negative. From 2008 to 2012 (table 1), Portugal and Greece appeared with the lowest market growths (-20.3% and -25.%, respectively) compared with countries like Austria, Belgium and Czech Republic with a positive market growth of 7.6%, 7.3% and 27.5%, respectively. (5,7,18)

Table 1: Total Pharmaceutical Market in Europe, 2008-2012 (19)

PAÍSES	2008	2010	2012	Growth (2008-2012)
Estonia	141	192	222	57.4%
Romania	1.914	2.113	2.627	37.3%
Bulgaria	617	671	795	28.8%
Czech Republic	1.832	1.976	2.335	27.5%
United Kingdom	12.826	13.583	15.035	17.2%
Italy	17.824	19.909	20.172	13.2%
Sweden	3.172	3.172	3.509	10.6%
Lithuania	436	479	482	10.6%
Denmark	2.006	2.150	2.202	9.8%
Cyprus	188	200	203	8.0%
Austria	2.921	3.022	3.142	7.6%
Belgium	4.189	4.428	4.494	7.3%
Finland	1.978	2.005	2.068	4.6%
Slovakia	1.057	1.092	1.102	4.3%
France	26.196	27.334	27.201	3.8%
Latvia	291	276	301	3.4%
Ireland	1.760	1.766	1.818	3.3%
Poland	5.014	5.016	5.080	1.3%
Slovenia	493	519	495	0.4%
Germany	26.523	27.022	26.184	**-1.3%**
Croatia	682	598	670	**-1.8%**
Netherlands	4.680	4.686	4.545	**-2.9%**
Hungary	2.091	2.064	2.005	**-4.1%**
Spain	13.949	14.858	13.181	**-5.5%**
Portugal	**3.660**	**3.428**	**2.916**	**-20.3%**
Greece	5.573	5.047	4.153	**-25.5%**

These results reflect the R&D investment. Countries with a strong tradition in R&D investment are the ones that have a big share of GNP (Gross National Product) percentage given to R&D investment and are the ones with highest market growth and market share. Portugal is one of the countries with the lowest investment in R&D. As a consequence, the number of clinical trials submitted in Portugal is lower than the number submitted in other countries. In 2010, Portugal had the lower ratio of clinical trials per million inhabitants (figure 10). (5,17,18,20)

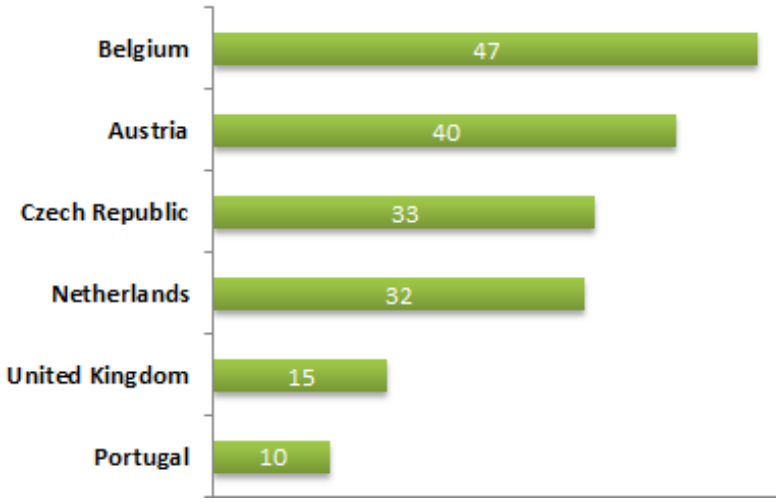


Figure 10: Number of Clinical Trials authorized per million inhabitants (2010) [Adapted from (18)]

Along with a low number of clinical trials, comes lower investment from sponsors. Table 2 compares the active clinical trials, number of sites, number of patients and the total investment in Portugal, Austria, Belgium and Czech Republic. Comparing Portugal with these similar countries, in terms of number of inhabitants, the difference of investment is evident. (5,17,18)

Table 2: Active Clinical Trials (2009) [Adapted from (21)]

Countries	Active Clinical Trials	Number of Sites (planned)	Number of Patients (Planned)	Investment (Million €)
Portugal	147	461	3917	58.755
Austria	188	596	6502	97.530
Belgium	328	1024	12996	194.940
Czech Republic	218	967	15433	231.495

This difference of investment is a consequence of the number of planned patients. Portugal has the lowest number. The number of patients per clinical trial and the number of patients in clinical trials per million of inhabitant in Portugal (figure 11) reflects their difficulty to recruit patients for clinical trials. Portugal has fewer patients per clinical trial and fewer patients in clinical trials per million of inhabitant (figure 11) than Belgium, Austria and Czech Republic. When compared with Belgium, Portugal losses more than €136 million in investment. (5,17,18,21)

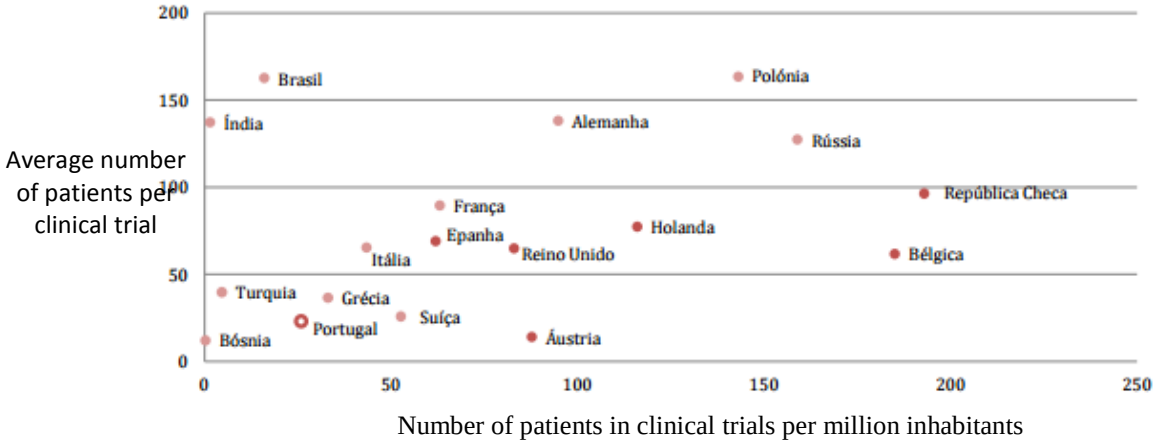


Figure 11: Recruitment Capacity per Clinical Trial, 2005 to 2011 (18)

Despite their compliant sites with qualified infrastructures, the organization of time resources and awareness of health professionals, Portugal is still far from perfect. There has been a trend for selection of Portuguese sites only for later development phases or observational studies (table 3). (5,18,19,22)

Table 3: Number of Clinical Trials by Development Phase in Portugal [Adapted from (19)]

	2007	2008	2009	2010	2011	2012	2013	2014
Phase I	7	3	6	2	6	3	10	10
Phase II	30	31	27	17	19	25	20	24
Phase III	74	100	73	79	58	82	75	81
Phase IV	21	12	9	9	5	8	9	12
Total (submitted and valid)	**132**	**146**	**115**	**107**	**88**	**118**	**114**	**127**

The lack of investigators motivation to promote more audacious and innovative therapies can explain large part of the prevalence of late phase clinical trials. Spain and United Kingdom, for instance, have a higher number of “academic trials” of investigator initiative than Portugal, which represents even ¼ of the number of their clinical trials, in 2010 (figure 12). (18,19)

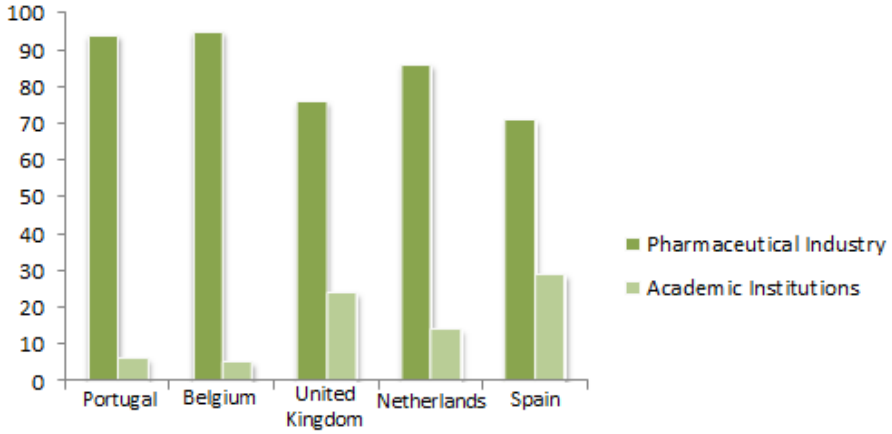


Figure 12: Proportion of clinical trials by type of sponsor, 2010 (19)

The bureaucratic burden of medicines development process with lengthy approval times is the biggest reason to the loss of Portugal's competitiveness. The real start time of a clinical trial, from submission to patient inclusion can reach extreme durations. As a result, when Portugal begins patients' recruitment, some international sites may be in the last visit of the last patient. (4,7,18)

In Portugal, the bureaucracy issues are distributed by four process entities: national authority (INFARMED), central ethics committee (CEIC), data protection authority (CNPD) and hospital management boards. (23,24)

CNPD is the main responsible for lengthy approval timelines. The Directive 2001/20/EC does not require the opinion of data protection experts. However, according to Portuguese legislation, the beginning of any clinical study is dependent of a CNPD positive opinion. CNPD is a ruler entity for multiple issues related to data protection, from book copyrights to sensitive clinical data. Nevertheless, CNPD has no experts in health area. As a result, CNPD usually asks for the same clarifications required by CEIC, which are already approved. It is important to review the role of CNPD. The inexistence of a dedicated regulatory body for clinical trial data related issues is therefore a great disadvantage. (7,23,27,28)

The negotiation between sponsors and sites also contributes for clinical trial beginning delay. Financial contracts state the financial terms and other details between relevant parties involved in clinical trial performance. Financial contracts should be in place prior to the initiation of any study and should be approved by CEIC. In Portugal, the time for this negotiation is very long. It is imperative to improve the flexibility in the negotiations between sponsors, CROs and sites. It would be certainly useful the existence of a financial contract model that could regulate the negotiations even between different sites. The cooperation among all stakeholders is of utmost importance. (23,26)

In sponsor perspective, time is recruited patients, recruited patients are results and if national sites keep delivering bad results the investment displacement is a logical consequence.

Other problems arise from the low level of involvement in academic research of the vast majority of potential development sites. The “academic essays” in Portugal are being conducted mainly in Hospitais da Universidade de Coimbra (HUC), Hospital de Santa Maria (Lisbon), Hospital São João (Porto) and in Instituto Português de Oncologia (IPO) of Porto and Lisbon. This fact explains the quality of the investigator’s training in Portugal. However, greater dispersion of the activity is necessary in order to reduce the dependence on a small number of sites, increasing the alternatives available to patients and health professionals, and recruitment rates. (18,30,31)

In addition to that, in Portugal there are no specific laws about clinical trials advertising and it is applied the legal framework of medicines. In “Estatuto do Medicamento” (Statute of Medicines) can be found the regulations for public advertising and advertising for health care professionals. These rules are very restrictive. It is necessary to create specific legislation for clinical trials advertising in order to inform society about ongoing clinical trials and, consequently, increase the recruitment potential. (23,29)

Despite these disadvantages, Portugal has some competitive advantages when compared to economic similar European countries. In addition to the commitment of clinical research teams, the quality of the investigator’s training is also very positive. This can be seen as one opportunity to develop credible clinical research. Another possible advantage of developing new medicines in Portugal lies in the fact that, by European levels, the practiced salary and the overheads are very competitive and allow an interesting cost-benefit relationship for sponsors. (7,18,19)

So, there is a strong potential for more Clinical Trials in Portugal, if the barriers of Portugal’s competitiveness are overcome.

The first step to overcome Portugal’s position on the global investment in Health was achieved in the last year, with “Lei nº 21/2014 de 16 de abril” approval. This law reduces the approval times from 60 days to 30 days, for both INFARMED and CEIC, and it was stressed the need for both agencies work together in their responsibilities. This law also establishes 15 days for financial agreement approval by investigational sites. As a result, the process can be shorter and truly parallel and ideally evaluated in one single instance. (23)

Even so, there is much work to do not only to drive public opinion and social awareness for the importance of clinical research, but also to develop more excellence sites, with highest quality standards. Clinical trials allows (1) patient access to new health technology, (2) better patient’s health monitoring practices, (3) increases health professional’s qualification and promotes

employment, (4) represents an alternative financial source for hospitals and investigational sites, and (5) represents an important investment in the country (figure 13). (4,17,18)

Figure 13: Clinical Trials economic value, 2012

The total investment in 2012, in Portugal, was €36 million that correspond to €3.6 per capita. In EU, the investment was €20,000 million. This corresponds to €40 per capita. If Portugal would be in the EU average the investment would be about €400 million instead of €36 million (figure 13). (18)

The economic value of clinical trials has a very relevant impact on Portuguese economy. In 2012 the market value was €36 million, with a direct gross value added of €21 million and €7.5 millions of tax revenues. The value of exports resulting from the clinical trials rose to €33 million, which contributed for less public spending, saving €3.5 million to the State and we also had, in 2012, 1086 jobs dedicated to clinical trials. The global impact on Portuguese economy can be evaluated using GNP multipliers. For the clinical trials area, this multiplier is €1.98, which means that every €1 investment generated in clinical trials activity provides a return of €1.98 for the general Portuguese economy. This puts clinical trials on the top 10 for the activities with better return.

Multiplying the factor of multiplication for clinical trials with the market value of this activity we obtain the total impact of clinical trials in Portuguese economy, which was €71 million in 2012. (7,18)

Definition of a strategic frame of work and a political agenda for clinical trials, review financial incentives and financial programs for clinical research, creation of specific legislation for clinical trials advertisement, improve conditions for clinical trials in primary care, adapt health professionals career and work schedule to clinical research are some proposals for a new future for Clinical Trials in Portugal. (18)

1.3 Internship Objectives

This section presents my objectives as a trainee in a Full-Service CRO (Eurotrials, Scientific Consultants) and in an investigational site (2CA-Braga).

The general objectives of my internship were to consolidate the knowledge and tools acquired in the Biomedical Sciences Degree and the Master's Course in Pharmaceutical Biomedicine, through the experience acquired from working as a collaborator of a Full-Service CRO and a study coordinator in an investigational site. More specifically, the objectives of my internship included:

Primary Objectives:

- Become familiarized with the real standards and procedures involved in the implementation and management of a clinical study and identify specific needs of different players.
- Collaborate in different scientific areas of a Full-Service CRO, get to know different areas of expertise.
- Gain experience as a study coordinator and participate in qualification visits, site initiation visits, monitoring visits, close-out visits and investigator meetings.
- Acquire the necessary knowledge to complete eCRFs.
- Participate in the conduction and preparation of audits and/or inspections.
- Understand the communications' flow of clinical trials' approval processes in a clinical research site.

Secondary Objectives:

- To apply and complement the theoretical background acquired during the first year of my Master Course and Biomedical Sciences Degree.
- Strengthen personal skills such as organization, communication and teamwork, as well as the capability of solve problems and think critically.
- Be capable of handle several tasks and projects simultaneously and prioritize them.
- Efficiently manage deadlines.

1.4 Overview of Host Institutions

1.4.1 Eurotrials, Scientific Consultants

1.4.1.1 Contract Research Organisations (CROs)

Pharmaceutical Industry has been experiencing significant structural changes. The globalization and the economic crisis over the last couple of years have been increasing the outsourcing of several services, including development of medical products. CROs, as Eurotrials, are increasingly assuming responsibilities in this area, particularly in the Biotechnology sector, where outsourcing has increased dramatically. These companies are scientific organizations (commercial or academic), to which a sponsor may transfer responsibility for some of its tasks or obligations.

A substantial growth has been observed in this business. It is estimated that more than 60% of all clinical studies now involve significant outsourcing. (2,33,34)

CROs can complete drug development tasks faster than the sponsors, without compromising data quality, even with larger trials, involving multiple study sites. This is a significant advantage, financially speaking, as taking a month off development time may result in an additional €27,6 million income (approximately) for pharmaceutical or biotechnology companies.

Topics of CRO input can range from "manufacturing and quality control to preclinical pharmacokinetic, pharmacology and toxicity studies; from the design, conduct and analysis of sophisticated Phase I and Phase II pharmacokinetic/pharmacodynamic decision making studies to manage multicenter studies; or from quality assurance to database management, statistical analysis and reporting". Nowadays, complete development programs are being designed and implemented by CROS (full service CROs) in collaboration with the corporate sponsor.

A full service CRO, as Eurotrials, has the resources to take on a development project in any therapeutic area at the preclinical phase and take it through to marketing approval. These CROs are similar to large pharmaceutical companies with all the same types of staff and systems, only without discovery research or a pharmaceutical sales force. (33,34)

1.4.1.2 Eurotrials Structure and Organisation

My internship began in Eurotrials (Scientific Consultants), a Portuguese owned full-service CRO. This is a private company created in Lisbon, in 1995 by members from different backgrounds in the academia, medical community and pharmaceutical industry. Eurotrials provides outsourced pharmaceutical research services for pharmaceutical and biotechnological industries, as well as consulting and training services.

Eurotrials operates in Europe, Latin America and Africa markets. It has also partnerships in Portuguese-speaking African countries since 2004. Its partners include pharmaceutical and biotechnology industries, CROs, regulatory agencies, food industry, academia and clinical research centers. (35)

This Full-CRO is organized in ten main departments which communicate and interact with each other on a daily basis, including: Research & Development (R&D); Clinical Trials; Epidemiology & Late Phase Research; Data Management; Biostatistics; Regulatory Affairs; Pharmacovigilance; Pharmacoeconomics; Quality; and Teaching & Training departments. (35)

With expertise in clinical research and scientific consulting in Health Sciences, this CRO was important to begin my internship since it gave me an overview of the roles and responsibilities of

different players involved in clinical research, as well as the main requirements and applicable regulations. In Eurotrials, I participated in different studies as a clinical trials assistant (CTA) of the clinical trials department, and also in some projects of the R&D department. These activities are described in more detail in chapter 2.

The clinical trials department is the biggest sector in Eurotrials. This department is responsible for clinical trials design; development of Case Report Forms (CRFs), with the collaboration of data management department; site selection for the trial; study monitoring activities; project management activities; and clinical report development, with the input of medical writing activities. Early planning of a clinical study is the focus of the R&D department. Meetings with Academia representatives, pharmaceutical companies and other CROs are some of the responsibilities of this department. The objective of these meetings is to develop business connections, new research projects and search for potential sponsorships, as well as strategic and regulatory planning of clinical studies, along with the clinical trials and Regulatory Affairs departments. (35)

In 2015, Eurotrials suffered a reorganization of its departments and its structure. This full-service CRO was reorganized in nine departments. Clinical Trials, Quality Services, Regulatory Affairs, Pharmacovigilance, Epidemiology and Late Phase Research, Data Management, Biostatistics and Health Economics departments were maintained. Research & Development and Teaching & Training departments disappeared and a medical writing department was created. Despite this reorganization, the main services provided by Eurotrials are the same. At this time, the trainee was no longer part of the Eurotrials' team.

1.4.2 2CA-Braga

Once Eurotrials' internship ended, I began my journey in an investigational site: The Clinical Academic Center – Braga (2CA-Braga) created in January 2012.

2CA-Braga is a non-profit partnership between the Hospital of Braga and the University of Minho, through the Life and Health Sciences Research Institute (ICVS) of Health Sciences School.

This research center has a registered office in Hospital of Braga, offering an ample, fully equipped and quiet space for physical/clinical evaluation, as well as support of nursing and administrative personnel for clinical trials. This support works in close proximity with clinicians, who provide hands-on knowledge on relevant clinical issues, study populations, feasible interventions and study design.

2CA-Braga stands on the interface between clinical and academic research. Its main objective is to contribute to the transference of knowledge from the bench of biomedical and technology

laboratories (university research: non-clinical trials) to the hospitals and clinics (clinical trials) and, in the end, to the market. (36)

The 2CA-Braga daily activities are ensured by its professional and experienced team in the field composed by study coordinators (one study coordinator manager in daily contact with the president of 2CA-Braga direction, and two other study coordinators responsible for different services of Hospital of Braga), study nurses, study pharmacists and financial and administrative assistants.

Study coordinators support the clinical research projects to be implemented in 2CA-Braga, as part of the investigational team, in different stages of the projects management. They are involved in the collection and management of clinical research data, perform study specific procedures and support monitoring activities. Study coordinators are also responsible for guidance and management of research team members, including study nurses, study pharmacists, laboratory and radiology technicians and other departments involved in that particular research project.

Study nurses are responsible for study activities related to the safety and well-being of study participants and protocol compliance. Vital signs assessment, samples collection and processing, and telephone contacts with patients (follow-up visits or schedule of study visits) are some examples of study nurses' daily activities in 2CA-Braga.

Study pharmacists coordinate and oversee the management of investigational products, including storage, preparation, accountability, dispensing and record keeping.

Financial and administrative assistants are responsible for submission processes to 2CA-Braga, financial activities (e.g. payments to research team members and patient expenses processing), and administrative and organizational aspects.(36)

In 2CA-Braga, I assumed study coordinator activities, under the supervision of Mónica Gonçalves (study coordinator manager) and financial activities related to contract negotiation, under the supervision of Cristina Rocha (responsible for contract negotiation in 2CA-Braga). These activities are described in more detail in chapter 2.

2. On-The-Job Training Activities

This internship can be divided in two phases. The first one lasts two months (August to September) and took place at Eurotrials. The second phase lasts seven months (October to April) and was mainly focused on common study coordinator activities in 2CA-Braga.

The training activities performed in these two organizations are described in next sections: Eurotrials' Training Activities and 2CA-Braga Training Activities.

2.1 Eurotrials Training Activities

The first weeks of this internship in Eurotrials were dedicated to self-training about clinical research regulatory affairs (applicable laws and regulations), clinical trials activities (qualification visits, SIVs, monitoring and close-out visits, safety procedures, audits and inspections); and its transcription into Eurotrials' standard operating procedures (SOPs). The quality manual of Eurotrials was also explored.

After this intense self-training phase, I became part of some R&D and Clinical Trials departments' projects. R&D activities include the participation in some projects and virtual meetings between Eurotrials and a client (2CA-Braga), under the supervision of Filipa Bernardo, Head of R&D department. In Clinical Trials department, I was part of diverse monitoring activities, since identification of sites and qualification visits until its close-out activities, under the supervision of Raquel Reis, Head of this Department.

2.1.1 R&D Training Activities

As mentioned before, one of the R&D department purposes is the establishment of partnerships with pharmaceutical companies and basic research institutions. Eurotrials and 2CA-Braga partnership is one example. I collaborated in one of the projects of this partnership: the development/improvement of the 2CA-Braga quality management system (QMS), which continued until the end of this internship in 2CA-Braga.

a) Development/Improvement of 2CA-Braga QMS

There is an increasing focus on having quality systems in place in the organizations involved in clinical research. Such systems require the development and implementation of standards for each step.

Investigational sites are highly regulated and require standard operating procedures and/or work instructions to streamline operations, while meeting the international standards and regulations.

So, the research teams should be trained on clinical research regulations and good clinical practice (GCP) guidelines. Research teams should also be trained on each clinical trial protocol. (37–39)

As a result of increased regulations and complex clinical trial protocols, there is a greater probability of research teams incurred in noncompliance situations. Without well-documented standard operating procedures, the risk for noncompliance situations further increases. Incomplete regulatory documentation (e.g. non-trained/unauthorized staff performing clinical trials activities), lack of clinical research training, lack of clinical trial protocol training or incomplete record keeping (lack of good documentation practices) are some examples of noncompliance issues.

To mitigate risk and noncompliance situations, investigational sites should consider using a systematic approach to conduct clinical trials by following eight principles of quality management systems:

- Principle 1: Customer focus
- Principle 2: Leadership
- Principle 3: Involvement of people
- Principle 4: Process approach
- Principle 5: System approach to management
- Principle 6: Continuous Improvement
- Principle 7: Factual approach to decision-making
- Principle 8: Mutually beneficial supplier relationships

By adopting and implementing a QMS program-wide approach, the investigational site can identify noncompliance issues as they happen, while investigating, correcting or preventing noncompliance issues in real time. (37–40)

To develop a QMS, an independent team should be identified to conduct a current state assessment of investigational site activity, including its noncompliance issues. Once this assessment is complete, a quality manual, standard operating procedures (SOPs), job descriptions (personnel roles and responsibilities), work instructions and supporting documentation, as flowcharts and quality records, should be created/improved. These tools must be in accordance with the quality policy of the investigational site. They should be consistent, coherent and should be easily accessible to all applicable staff members. These documents should be revised as needed and stored according to good documentation practices. (37,39,40)

During my internship, I participated in the revision of some of these documents, namely the quality manual and job descriptions documents of 2CA-Braga QMS. Collaboration protocols and confidentiality agreements were also created for 2CA-Braga QMS and reviewed by me.

The quality manual is an official document that details how institution's quality management system operates. This manual includes information about institution's organization (including organizational charts); institution's mission, vision and values; institution's code of conduct; quality policy; and institution's QMS organization (including procedures for training, quality control and assurance). The quality manual is a living document suffering changes whenever considered important to fit institution's necessities and goals.

The investigator, sub-investigator, study coordinator, study nurse, study pharmacist, and all other staff involved in clinical trials in 2CA-Braga should understand and accept their roles and responsibilities, by signing a job description, a collaboration protocol and a confidentiality agreement. This documents must be in accordance with regulations, international guidelines (e.g. International Conference on Harmonization guidelines), as well as, internal policies and procedures of the institution. (39,40)

My participation in this project began in Eurotrials and continued until the end of this internship in 2CA-Braga in April. In Eurotrials, I was responsible for preparing collaboration protocols, confidentiality agreements and job descriptions for each staff member of 2CA-Braga, according to their role and responsibilities. In 2CA-Braga, I discussed and reviewed these documents with each staff member, since they are specialists in their activities. According to staff members' feedback, I updated these documents when needed. The quality manual was also reviewed and updated accordingly.

By utilizing the QMS approach, the research teams remain well-trained in clinical research policy and also in clinical trial protocol procedures, which leads to increased productivity, the delivery of the highest safety standards and quality clinical trials activities. (37)

2.1.2 Clinical Trials Training Activities

According to ICH-E6 GCP guideline, a clinical trial is "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy". (25)

New medicines or medical devices must prove its safe and effectiveness before being marketed. Clinical trials are the fundamental tool of therapeutic evaluation, being essential for this purpose. They should be conducted in accordance with the ethical principles that have their origin in the values outlined by the Nuremberg Code, Belmont Report and Declaration of Helsinki for human

subjects research. Clinical trials must also comply with the International Conference on Harmonisation (ICH) guidelines such as GCP and with the applicable regulatory requirements. (23,25,28)

As explained in state of the art, clinical trials can be divided in four phases: phase I studies (or human pharmacology trials), phase II studies (or therapeutic exploratory trials), phase III studies (or therapeutic confirmatory trials), and phase IV studies (or therapeutic use trials) (table 4). (1,9,10)

Tabela 4: Clinical Trials Classification [Adapted from (2)]

STUDY PHASE	CHARACTERISTICS OF STUDY
PHASE I (Human Pharmacology trials)	• Assess tolerance and safety • Define/describe PK and PD • Explore drug metabolism and drug interactions • Small study group of 20-100 healthy volunteers • Studies typically lasts several months
PHASE II (Therapeutic Exploratory trials)	• Establish safety profile • Explore use for the targeted indication (efficacy) • Estimate dosage for subsequent studies • Provide basis for confirmatory study design, endpoints and methodologies • Randomized and blind testing, where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. • Study group may include up to several hundred patients • Studies may last several months to a couple of years
PHASE III (Therapeutic Confirmatory trials)	• Demonstrate/confirm effectiveness • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Randomized and blind testing • Study group may include several hundred to several thousand patients • Studies last several years • Once completed, FDA or EMA's approval can be requested to marketing the drug
PHASE IV (Therapeutic Use or Post Marketing Surveillance trials)	• Conducted after a drug or device approval for marketing • Compare a drug with other drugs already in the market • Monitor a drug's long-term effectiveness and impact on a patient's quality of life • Determine the cost-effectiveness of a drug therapy relative to other traditional and new therapies

The planning, implementation and submission of these clinical trials are highly regulated, including: European Commission Directives:

- 2001/20/EC of April 4th: establishes specific provisions regarding the conduct of CTs on human subjects involving medicinal products, relating to the implementation of GCP. This Directive does not apply to non-interventional trials. (28)

- 2005/28/EC of April 8th: lays down the principles and detailed guidelines for GCP as regards IMPs for human use, as well as the requirements for authorization of the manufacturing or importation of such products. (41)

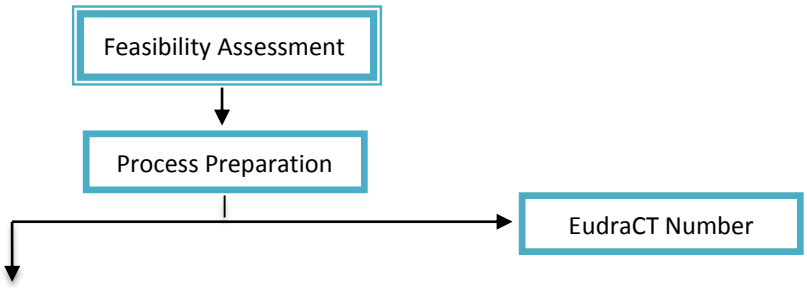
National Law:

- Law no 21/2014 of April 16th: transposition of Directive 2001/20/EC of April 4th and Directive 2007/47/EC of September 5th, the latest concerning medical devices. (23,24,42)
- Decree-Law no 102/2007: transposition of Diretive 2005/28/EC
- "Portaria nº 57/2005" of 20th August: approves the functioning of CEIC, which ensures protection of participants' rights, safety and well-being during CTs. (26)
- Law no 67/98: regulates CNPD activity and establishes guiding principles of the processing of personal data, ensuring participants consent and confidentiality issues. (43)

Other essential documents:

- Declaration of Helsinki (2013): definition of ethical principles for medical research involving human subjects. (44)
- ICH guidelines: harmonization of requirements for registering medicines in Europe, Japan and United States. Although all applicable guidelines should be followed, one should be highlighted:
  - ✓ ICH-E6 – GCP: international pattern of requirements of ethical and scientific quality that must be respected in the development, implementation, submission and reporting of clinical trials. (25)

In Portugal, clinical trials need to be previously approved by the National Authority of Medicines and Health Products (INFARMED), the Commission of Ethics for Clinical Research (CEIC) and the National Committee for Data Protection (CNPD) (figure 15). (23,26,43)



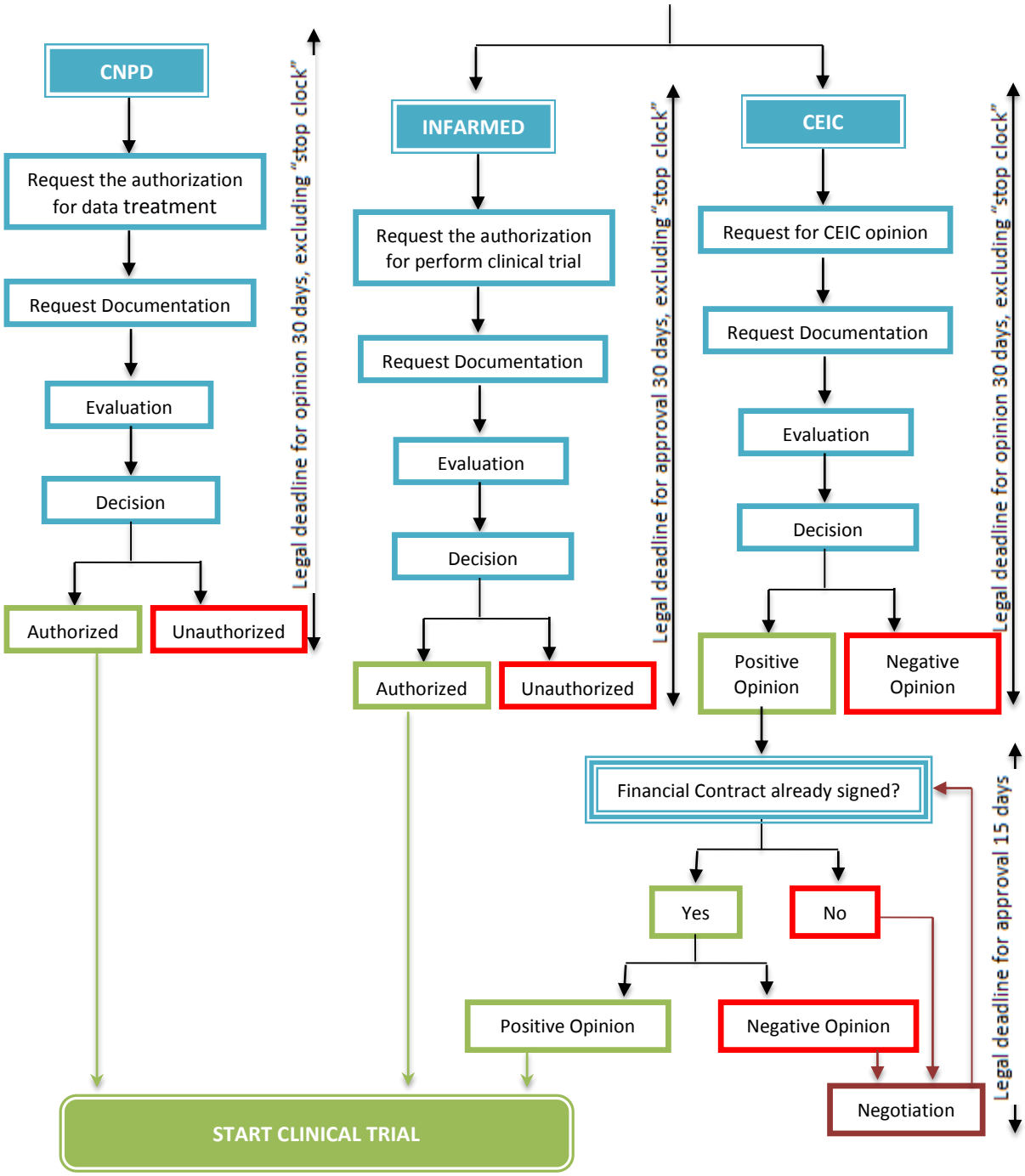


Figure 14: Approval Process for Clinical Trials in Portugal [Adapted from (7)]

The Clinical Trials department of Eurotrials is constituted by one country clinical trials manager, CRAs (or monitors) and CTAs. I assumed CTA activities.

CTAs main responsibility is to ensure administrative support to CRAs. CTAs fill study documents, manage study documentation and prepare dossiers for on-site visits and investigator's meetings.

CRAs are responsible for supervise the overall conduct of the trial. CRAs ensure that trials are conducted and data are generated, documented (recorded) and reported in compliance with the study protocol, GCP, and the applicable ethical and regulatory requirement(s). (1,9)

CRAs are also the main liaison between investigators and sponsor. They assist the sponsor in selecting appropriate sites for that specific study and perform pre-study visits to assess the investigator's interest and the adequacy of site's infrastructures and human resources for that trial. After site's selection, the CRA follows it from start to finish, working in the office and in sites, by carrying out on-site or remote visits, respectively. On-site visits can be divided, according to the time progression of the trial, as:

- Pre-Study Visits (or Qualification Visits): Depending on the sponsor, these visits can be in-person pre-study visit (PSV) or remote visits (via telephone or web conference). Review the adequacy of the site, the training and experience of the study staff, the access to the right patient population, and the site's interest in the study are the main objectives of a pre-study visit.
- Site Initiation Visit (SIV): During an initiation visit a great deal of time is spent in training or reviewing the study protocol design and answering questions from the site personnel. The investigator's responsibilities, study procedures, IP management, documentation responsibilities, CRFs are some mandatory aspects that need to be discussed in SIVs. At this time point, the site must be ready to start the trial. Study medication and materials must be available and required documentation complete and available. This meeting should be attending by all members of the study team.
- Routine or Interim Monitoring Visits: These visits include any visit that occurs after the site is initiated and up until the site is close out. The main purpose of these visits is to protect subject safety by monitoring the trial conduct for ICH/GCP compliance. Furthermore, these visits allow an in-process quality control of study data (source data verification - SDV). During these visits, CRAs (or monitors) ensure that:
    - sites are compliant with all study requirements;
    - subject safety is being adequately followed;
    - data is being reported in a timely and reliable manner;

- the IP is being handled as per protocol and relevant regulations/guidelines;
- there are no significant deviations from the planned study protocol;
- all important study documentation is being generated and stored properly; and
- research site is adequately supplied in regards to lab kits and other pertinent study materials.

- Close-out Visits: A close-out visit should occur when subjects are no longer being dosed, all the data have been collected (there are no more outstanding AEs/SAEs, queries/data clarification forms), the database is locked and ready for statistical analysis, and the study conduct has ended. The whole concept of a close-out visit is to ensure that documentation is well organized and will remain intact and be accessible in the future as needed for regulatory reasons. A sponsor or regulatory authorities should be able to return to the site years later and re-create exactly what occurred at all points during the trial by reviewing the regulatory documentation, subject and source documentation, full medical charts, and any other applicable study records. Documentation is everything in pharmaceutical industry ("if it isn't documented it didn't happen"). Close-out activities include site supplies return and medication reconciliation, review of essential documents (subject identification list, subject screening and enrollment log, informed consent forms, delegation of authority log, accountability logs, protocol/amendment signature pages, etc) and source documentation (lab reports, AEs/SAEs and its clinical significance assessment, etc.).

After these visits, CRAs must prepare a visit report for the sponsor and a follow-up letter to the site. (1,9,45)

a) Activities developed as CTA in Clinical Trials Department

As CTA in Eurotrials, I had the opportunity to participate and collaborate in qualification visits, SIVs and monitoring activities performed by an experienced CRA.

In the qualification visits, I was just an observer. Firstly, the CRA scheduled these visits with PI and SC and sent them a qualification visit agenda with the main issues that would be discussed. These visits were performed on-site in two different hospitals, one of these sites had study coordinator (SC) and the other one had no SC. This difference is crucial to decide which sites should be selected, and particularly to the clinical trial in question. These qualification visits were related to a clinical trial protocol in chronic kidney disease with demanding procedures, since the first eight visits would be weekly, the next four visits would be bi-weekly and the other visits would be monthly. As a result,

the time of research team to conduct the study would be an essential issue to site selection, in addition to site's infrastructures and study staff experience and training.

During these qualification visits, the CRA presented an overview of study population (eligibility criteria), study procedures and its critical milestones. The main concerns and questions of each PI about this trial were debated and the conclusions would be discussed with sponsor. If appropriate, the sponsor would amend the protocol accordingly. Based on the CRA presentation, each PI committed himself with a specific number of patients that he would include in the study. Pharmacy and laboratory of each hospital were also visited by CRA, to assess the adequacy of each site.

In the end of this visit, CRA wrote a qualification visit report to sponsor. The main difference between these reports was the existence of a SC and, consequently, the number of patients proposed by each PI to include in this study.

The SIV where the trainee had the opportunity to participate was related with the same study, in patients with chronic kidney disease.

As stated before, the main objective of a SIV is to train research teams in the study protocol. However, from qualification visits to site initiations visits and after, the study protocol is reviewed several times, according to trial results and safety issues that become available. So, the preparation and review of study dossiers and its documentation needed to train research teams and to conduct the study is essential, and should be performed before a SIV by CRA. I was responsible for these activities.

Firstly, the CRA explained to me the main points that would be discussed with the research team during this SIV and gave me a list with the documentation needed and their more recent versions. I collected and compiled all these documentation in a working dossier to CRA. This dossier also included prototypes of investigational products, patient cards, patient questionnaires, eligibility pocket flyers and mini protocols to show to research team, in order to involve them in this clinical trial since the beginning. I was also responsible for reviewing the ISFs (Investigator Site Files), Pharmacy Binders and study coordinators working dossiers, to ensure the inclusion of the last approved version of their documents.

Once all required approvals were in place and all study dossiers were created to the site, the CRA scheduled an Initiation Visit with the study coordinator of the site. A site initiation visit agenda was sent by CRA to PI and SC, who sent it to the other members of the research team. The SIV was scheduled soon before the anticipated activation date, so information discussed at this visit was retained by the research team. PI, study coordinator, sub-investigators and representatives from the supporting departments (including pharmacy, radiology and laboratory) were presented in this

visit. This meeting consisted in a protocol review and a detailed discussion of study implementation; study procedures review; data handling and electronic systems training; investigational product distribution and handling; specimen processing, storage and shipping procedures; safety reporting; good clinical practice training; sponsor and investigator responsibilities; and record retention. During this presentation, the prototypes were distributed among research team as appropriate. Based on study protocol and its procedures presented by CRA, investigators did some questions and discussed their main difficulties about patient recruitment and study conduct. The first weekly eight visits and demanding pharmacokinetic procedures were some examples. These difficulties would be discussed between CRA and sponsor, lately. In the end of this visit, the CRA asked for PI signatures and other research team members' signatures (present in the meeting) in some essential documents (e.g. delegation of responsibility/signature log, training log, site visit log, recruitment and retention plan form, source documents record form). In the end, CRA wrote a SIV report to the sponsor and a SIV follow-up letter to the site, with pending issues.

The periodic monitoring visit that trainee assisted was related with a different study, in patients with multiple myeloma.

The sponsor usually develops a monitor plan that includes the frequency and duration of periodic monitoring visits. In this study, the sponsor established a monitor plan of monthly visits from two to three days. CRA scheduled this visit with SC for three days, since the site had included eleven patients with monthly protocol visits.

In the first day morning, CRA reviewed the pharmacy records to ensure proper investigational product storage, handling, disposition and accountability documentation. The IP containers were also assessed by CRA to ensure protocol compliance with study dosing schedule. No discrepancies were founded by CRA.

In the other two days, the monitoring activities included: assessing protocol adherence, compliance with ICH/GCP and/or regulatory requirements; evaluating subject enrollment; verifying signed consent documents, eCRFs (start & stop dates of adverse events, concomitant medications and study medications review) or data queries; performing source document verification (laboratory reports and X-ray scan reports reviewed and signed by PI, procedures documenting study parameters reported in eCRFs, informed consent process documentation); ensuring all AEs and SAEs are reported in accordance with applicable regulatory requirements reviewing regulatory documents/Investigator Site File; enssuring proper collection, processing, storage and shipment of laboratory specimens.

The records from enrolled subjects were reviewed for protocol adherence. Protocol deviations and its record on eCRF were also reviewed. The inclusion/exclusion criteria and subjects' eligibility were assessed by CRA to confirm that subjects met enrollment criteria, since the eleventh patient has been included in the week before. eCRFs and subject medical records were reviewed with SC and PI to address and discuss data discrepancies and findings detected by CRA. Site's responses to data queries were also reviewed to verify that the data correction performed in response to the query was accurate and complete. AEs and SAEs were reviewed to ensure that they were reported within the defined protocol requirements and required regulatory guidelines. The Investigator Protocol/Regulatory File Review included the revision of *curriculums vitae* (CV) and medical licenses available on ISF to ensure that they were updated (signed and dated within two years of the study start date). CVs and medical licenses would be maintained for the duration of the study and its expired versions would remain in the file to document valid licensure at the start of the study. CRA also reviewed FDA Form 1571 to ensure that it was completed, up-to-date and signed by PI.

At the conclusion of this visit, CRA performed a summary meeting with PI and SC to review the findings and discuss recommendations. This meeting provided an opportunity for immediate dialogue, feedback, clarification and education to the site. During this visit, CRA reviewed visit findings with the site so that they were made aware of the key issues found during this visit and that would require a continuous monitoring from the site.

Monitoring visit findings and resulting action items were documented in a monitoring visit report sent to the sponsor. A follow-up letter with findings and pending issues was sent to the site for review and placed in the ISF.

These activities developed as a CTA in Eurotrials were very important to my internship in 2CA-Braga as a clinical trials coordinator. Based on the qualification and site initiation visits assisted as a CTA, I understand the importance of preparing these visits in advance to save time and avoid pending issues. CVs and GCP certificates of research team members, calibration certificates of all site and pharmacy equipment used in clinical study conduct, normal values/ranges for lab tests & medical procedures, for instance, should be available on qualification and site initiation visits. My participation in monitoring visits was also very important to identify and understand the most common findings detected by CRAs during these visits, and avoid them during my clinical trials coordination activities in 2CA-Braga. The appropriate record of informed consent process in patient health records as well as other specific study visits procedures; the investigator validation of central and local laboratory results as well as other supplementary diagnostic procedures, and the update

of screening and patient identification logs are some examples of the activities that should be performed before a monitoring visit in order to avoid findings.

b) Development of a clinical trials database for site selection and qualification

Site Selection is one of the most significant factors for a successful clinical trial. It always depends on the specific design of the study.

First of all, the sponsor needs to decide on the geographical territory (which countries should be selected) and evaluate the potential sites available. The availability of specialized diagnostic and therapeutic equipment, a track record with previous and similar trials, the geographic location and regulatory history have to be taken into account by sponsor to country selection, as well as the number of available sites. Country selection strategies include reviewing regional epidemiological data or evaluating clinical data on existing patient populations.

Once country selection is completed and all potential sites are identified, the sponsor has to decide which sites should be opened and selected, based on protocol synopsis and study design. So, a feasibility questionnaire should be sent to all potential sites to evaluate its staff experience and training, and site's infrastructures. (1,9,45)

Getting the right results from a clinical trial starts with choosing the right site as its success is determined by the clinicians who recruit, enroll, treat and evaluate trial patients. The experience of site staff, such as investigators or study coordinators, the availability of suitable patients and the ability to perform required clinical assessments are essential and have to be considered when selecting a site. If there is staff available on the site, the sponsor has to evaluate their interest and motivation. If people are not motivated and not willing to participate, then they won't conduct a correct study.

Companies can improve site selection by working with a specialized team. Improvements in site selection can be achieved by using regional experience. In many cases, companies can get this experience from contract research organizations (CROs), using their network of relations. Eurotrials is usually contracted for these services. (7,9,18)

During my internship, the head of clinical trial department of Eurotrials (Raquel Reis) decided to improve site selection process, by creating an integrated clinical trials database. This database would include all information related to initial contacts with sites to evaluate their interest in participating in specific studies; feasibilities questionnaires and qualification/selection visits performed by Eurotrials. The trainee was responsible for imagine, create and complete this database for future site selection and qualification processes.

This integrated clinical trials database was performed in an excel document, where each line was related to a unique study. It was divided in four main “menus”: Sponsor Information, Overview of Study, Site Information, and Comments/Observations.

Sponsor Information “menu” included information about the type of sponsor (pharmaceutical industry, academic sites, other CROs, among others), name of sponsor and its contact information. Overview of study included information about title, phase, therapeutic area, study drug, and objectives of the study, as well as eligibility criteria information. Site Information “menu” consisted in site and its staff contact information, including principal investigator, study coordinator, sub-investigators and responsible of pharmacy, local lab and radiology department, as well as site responsible for contract negotiation and payments. Institutional review board/independent ethics committee information; interest in participating; patient population and recruitment potential; staff experience and training; study logistics and financial aspects of site were also included in Site Information “menu”. The Comments/Observations “menu” was a free text field to include some pertinent particularities about site or study to consider in future site selection or qualification visit processes.

This integrated clinical trials database allows Eurotrials to identify qualified investigators and sites based on previous clinical research experience.

My main difficulty during this project was to collect all the retrospective information needed to include in the database. Many feasibility questionnaires were incomplete and the missing information had been obtained by phone or e-mail by CRAs in the past. However, with the collaboration of those CRAs, the most important information was obtained and included in the database. I conclude that it is very important to adopt appropriate strategies to collect and record information in a reliable manner that could be tracked in the future.

2.2 2CA-Braga Training Activities

Clinical studies coordination was the main focus of my daily activities during this second phase of my internship in 2CA-Braga. At the same time, I was also responsible for the negotiation of financial agreements of different studies, including observational studies and phase II, III and IV clinical trials. Besides clinical studies coordination and contract negotiation, I had the opportunity to participate in the “1as Jornandas de Investigação Clínica e Inovação”.

2.2.1 Clinical Study Coordination Activities

A clinical study involves research using human volunteers (also called participants) that is intended to improve medical knowledge. There are two main types of clinical studies: clinical trials (also called interventional studies) and observational studies.

In a clinical trial, participants receive specific interventions according to the study research plan or protocol. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, such as diet. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients, or to no intervention. Some clinical trials compare interventions that are already available to each other. Investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants. For example, investigators may give a drug or treatment to participants who have high blood pressure to see whether their blood pressure decreases. Clinical trials are divided in four different phases, according to their clinical development phase or by their objectives and outcomes, as explained before.

In an observational study, investigators assess health outcomes in groups of participants according to a research plan or protocol. Participants may receive interventions (which can include medical products such as drugs or devices) or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator (as in a clinical trial). For instance, investigators may observe a group of older adults to learn more about the effects of different lifestyles on cardiac health. (1,9)

The clinical studies coordination activities performed during my internship were related to both observational and interventional studies (phase II, III and IV trials). In 2CA-Braga, I had the opportunity to participate in the entire life cycle of a clinical trial implementation and conduct, except in close-out activities. I had also no opportunity to participate in audits or inspections.

a) Activities related to Feasibilities Questionnaires and Qualification Visits

Conducting clinical study feasibility is one of the first steps in clinical study implementation. This process includes accessing internal and environmental capacity, alignment of the clinical study in terms of study design, dose of investigational product, comparator, patient type, with the local environment and assessing potential of conducting the clinical trial in a specific site.

When 2CA-Braga was identified as a potential site to conduct a specific study, the sponsor sent them an email with information about therapeutic area, study drug, study phase and its main objectives. A confidentiality disclosure agreement (CDA) was usually attached to these emails for PI signature. This CDA was signed when PI was interested in conducting the clinical trial.

In 2CA-Braga, the study coordinator manager assessed this email information and forwarded the email to the study coordinator responsible for that specific therapeutic area. I was responsible for cardiology, ophthalmology and dermatology departments, as well as some specific therapeutic areas in oncology department, including multiple myeloma and lymphomas. Alzheimer Disease studies were also my responsibility.

In the studies related with the therapeutic areas mentioned before, I was responsible for talking with its department director, who identified the principal investigator for the clinical trial in question. Then, I would talk with the principal investigator selected by his department director and asked him to sign the confidentiality agreement. This CDA was usually sent to sponsor in two or three days. After reception of CDA, the sponsor sent the feasibility questionnaire to me and PI. This feasibility questionnaire was discussed with PI and answered within three to five days.

Based on feasibility questionnaires responses, the sponsor would select some sites to perform qualification visits in order to review and assess the information collected in feasibility questionnaires.

Qualification visits usually consisted in a protocol overview about study population, study procedures and its critical milestones. In 2CA-Braga, PI, pharmacy representative and study coordinator were usually presented in these qualification visits scheduled between the sponsor's representative and trainee. In first qualification visits the study coordinator manager was also present. Today, I am able to conduct qualification visits alone with PI and pharmacy representative. Principal investigator answered CRA's questions about study population and potential recruitment, as well as research team experience and training. Pharmacy representative was responsible for pharmacy tours and answered CRA's questions about pharmacy infrastructures and organization, as well as pharmacy team experience and training. I (as study coordinator) answered CRA's questions about site's logistics and infrastructures, as well as other practical issues related to contract negotiation and payments processes, patients' expenses reimbursement procedures and institutional review boards. CVs of PI, pharmacy representative and study coordinator were usually given to CRA in these visits. The radiology department and local lab tours were also my responsibility.

b) Activities between a Qualification Visit and a Site Initiation Visit

In Portugal, to conduct a clinical study and to initiate a site, the sponsor has to obtain approval of all applicable competent authorities, including:

- INFARMED, CEIC and CNPD approval for clinical trials involving intervention; and
- CNPD and institutional review boards' approval for observational studies.

So, before a site initiation visit, the site has to work closely with sponsor to collect and make available the required information as soon as possible to clinical study approval.

Once selected, I (as study coordinator) received a confirmation letter of 2CA-Braga selection to conduct the clinical study presented in the previous qualification visit, as well as PI. This confirmation letter was followed by numerous emails from sponsor's representative, requiring documentation to initiate the study submission process, including:

- Pharmacy and Site Conditions Statements to document the availability of adequate infrastructures, as well as experienced and trained research staff to conduct the study;
- Investigator brochure signature page to document that relevant and current scientific information about the investigational product has been provided to principal investigator;
- Protocol signature page and amendments, if any, and sample case report forms (CRF) to document investigator agreement to the protocol, its amendment(s) and CRF;
- Financial aspects of the trial to document the financial agreement between the investigator/institution and the sponsor for the trial, including the financial contract and all financial disclosures regarding the investigator and the manufacturer of the product being studied;
- Dated, documented approval/favorable opinion of institutional review boards (when applicable);
- CVs, GCP certificates or other relevant documentation evidencing qualifications of investigators, sub-investigators and other research team members to document their qualifications and eligibility to conduct the study and provide medical supervision to subjects;
- Normal values/ranges for lab tests & medical procedures;
- Certification, accreditation or other validation of lab/facility to perform tests & procedures;
- Calibration certificates of all site and pharmacy equipment used in clinical study conduct.

During the approval process, the competent authorities can require some clarifications about this documentation. This was the case during a submission process of a study in dermatology. CEIC asked for more detailed information about the clinical trials mentioned by PI in her CV. I talked with PI, who gave me the titles of the studies. It was sufficient for CEIC.

When sponsor received the approval for conduct the study in 2CA-Braga, a site initiation visit was scheduled with research team. Before the site initiation visit, the SC's, nurses', pharmacist's and PI's usernames and passwords to eCRFs, IVRS/IWRS and other study specific platforms (e.g. platforms to review safety letters or to access patient's analysis results of central laboratory) were provided. The training in these platforms must be completed before the site initiation visit.

c) Activities related to Site Initiation Visits

The trial proceeds after obtaining the approvals and signed agreements. The sponsor, principal investigator and study coordinator should have access to a set of essential documents, which together form the Trial Master File (TMF).

When all approvals and signed agreements are obtained and the TMF is available at site, the site is ready to start the trial. A site initiation visit is scheduled with study coordinator, PI and the other members of research team.

During my internship, I had the opportunity to participate in numerous SIVs related to different therapeutic areas, such as atrial fibrillation, age-related macular degeneration, chronic urticaria, multiple myeloma, lymphomas, Alzheimer Disease, among others.

As mentioned before, the principal objective of these meetings is the training on study protocol. Study objectives; endpoints; eligibility criteria; study design and plan; screening procedures; randomization procedures; study procedures; informed consent process and informed consent forms; safety activities; end of treatment procedures; follow-up activities; end of study procedures; study withdrawal procedures; AEs and SAEs management and report; case report forms; source documents; GCP principles and investigator responsibilities were the main aspects discussed during these meetings. During this discussion, research team members had the opportunity to clarify their doubts/questions related to study protocol or procedures. PI, SCs, pharmacists, radiology technicians and at least two or three co-investigators of each research team were presented.

In the end of each SIV, the research team members signed training and delegation logs to document their training in the protocol and their responsibilities in the study. CRAs provided the study materials, including patient files, Informed Consent Forms (ICFs), patient cards, AE diaries and record worksheets.

Before living, CRA reviewed the pharmacy binders with pharmacists to ensure proper documentation of IP accountability, dispense and return. Clinical trial procedures about sample collection and processing, IP administration and data record were also discussed with study nurses.

Central laboratory kits, manuals and shipping materials available at site were checked by CRA to ensure the availability and adequacy of all material needed to start the study.

When all pending situations were resolved and all necessary documentation and materials were available at site, CRA sent an activation confirmation letter to the site. Once received the letter, the site was ready to begin the recruitment activities.

d) Activities between a SIV and Monitoring Visits

When a site activation letter is received, the recruitment of patients can begin.

To facilitate patient recruitment and the overall study conduct by investigators, as well as to ensure protocol compliance, patients' files were usually created. Depending on study sponsor, these patient's files could be prepared and provided by them. However, these dossiers were usually prepared by the SC of the site. I was responsible for the preparation of all patients' files related to the therapeutic areas of my responsibility (mentioned before).

These dossiers were usually divided in eight sections, including: informed consent forms, nursing records, visits' procedures, patients' health records, patients' analysis results of local laboratory, patients' analysis results of central laboratory, supplementary diagnostic procedures, and SAEs. The informed consent forms section included all original ICFs applicable to the study (e.g. general ICF, pharmacogenetic ICF, biological samples repository ICF, future biomedical research ICF, audio recording ICF, caregiver's ICF) signed by the patient and caregiver (when applicable). The nursing records included patients' vital signs of each visit such as temperature, weight, height, pulse, blood pressure, heart rate, respiratory frequency, as well as study medication administration times and its therapeutic unit numbers. The visit's procedures section was divided in sub-sections related to each visit required by study protocol. Each sub-section included a checklist of all required protocol procedures for that visit and all applicable worksheets, such as eligibility criteria worksheets, screening and randomization worksheets (in screening and randomization visits, respectively), prescription sheets, patients' questionnaires, AE diaries, among others. The other sections included patients' health records since their inclusion in the study; analysis results of local and central laboratory validated by investigators; supplementary diagnostic procedures reports assessed and validated by investigators; and SAEs reports signed by investigators.

When finished, these patients' files were presented to investigators and recruitment strategies were discussed with them. When a potential participant was identified, investigators gave me his/her contact information. Schedule of screening visits and screening exams, within required study windows, were my responsibility. The schedule of the other visits of the protocol and required

exams were also my responsibility. Each visit was scheduled by phone a few days before, and the patient was reminded to come fasted (as applicable) and to bring his/her patient diary (as applicable).

Screening visits were a little different from the other study visits. I had the opportunity to participate and collaborate in diverse screening visits. During these screening visits, investigator explained the clinical trial and its study procedures to the patient, clarified their doubts and emphasized that they could withdraw from the study at any time. The patient could take the ICF home and make a thoughtful decision. Another visit could be scheduled for any clarifications, and eventual inclusion of the patient in the clinical trial. After signing the ICF(s), if the study protocol allowed and the patient agreed, the screening visit could be performed in this same visit. Once the patient gave his/her consent, I (as SC) registered the patient in the IVRS/IWRS system, and obtained the patient's screening number, which identified the patient in the study. A screening confirmation was obtained by fax, email, or in the IWRS system. After obtaining the screening confirmation, the screening exams were scheduled within the required timelines. Investigators recorded the physical and clinical evaluations details, demographics, medical history and diagnosis in patients' health records, as well as other data usually recorded in all study visits. The informed consent process was also appropriate recorded. Then, study nurses collected urine and blood samples according to the central laboratory requirements and recorded patients' vital signs. The processing and shipment of screening urine and blood samples were responsibility of study nurses.

These screening visits were followed by the patient's randomisation/treatment initiation visits. During these visits, investigators evaluated the eligibility criteria: inclusion criteria and exclusion criteria. For this, investigators evaluated the results of the patient's screening exams and central laboratory results. There were other factors also considered by investigators, such as the patient's inability to fill in a diary. This could be an exclusion criterion, as it can mean non-compliance to the protocol. The eligibility criteria form is filled by investigators. If the patient did not meet the criteria, he/she was considered a Screening Failure and registered in the IVRS/IWRS system as a screening failure. If the patient met the criteria, he/she was randomised in the IVRS/IWRS system, and the patient was allocated to a treatment arm. The medication was assigned to the patient in the same system. The other procedures of these randomization/initiation treatment visits were similar to the next study visits as detailed below.

After screening and randomization/initiation treatment visits, the next visits were scheduled according to the study protocol timelines. The main objective of these visits was to evaluate the patient's status and receive or discontinue study treatment. Before usual medical examination,

patients answered all applicable study questionnaires and study nurses measured and recorded their vital signs. Urine and blood samples were also collected by study nurses according to laboratory study procedures. Their shipment to central laboratory was also responsibility of study nurses. Then, investigators evaluated patient's physical and clinical condition and recorded the data, including physical exam, concomitant medication, evaluation of laboratory results, signs and symptoms according to the "Common Terminology Criteria for Adverse Events" code and imaging evaluation (e.g. X-rays, PETs, CAT scans or MRIs) when available. ECGs (when applicable) were also performed and evaluated by investigators.

While investigators performed medical examination, I completed the IVRS/IWRS calling, which identify the medication lot number to dispense to the patient. In clinical trials with medication dispense and administration, a prescription worksheet (with medication lot number) signed by investigator was sent to the pharmacy. After several minutes, pharmacists delivered study medication to study patients for oral administration (when applicable) or to study nurses for preparation and intravenous, intramuscular or subcutaneous administration (when applicable), depending on the study protocol. When, by protocol, the patient took the study medication home, pharmacists explained them how to handle the study medication and the administration times and dosage. Details on the next appointment were discussed with investigators. Based on this discussion, I schedule the next study visit with patients and its required exams. In the end of the study visit, I asked patients to bring their expenses receipts in the next visit, to reimburse them. Processing the patients' expenses were not my responsibility, since 2CA-Braga has a financial administrative responsible for that.

After each visit, patients' data had to be reported on eCRFs (an electronic data collection platform provided by the sponsor of the study to collect participants' health information) within the timelines defined by the protocol (usually within five days after study visit). The data reported in eCRFs were based on patients' health records performed by investigators during study visits. These usual data included study disease status, study medication compliance, date of study visit, vital signs, laboratory results, imaging results, AEs, concomitant medication, questionnaires and other applicable information. These activities were my responsibility. eCRFs had to be a "mirror" of the patients' health records. If I detected inconsistences during data entry activities in eCRFs, amendments to patient's health records were necessary. Usually, I scheduled a meeting with investigators to discuss and amend these inconsistences and missing information between eCRFs and patients' health records. During my internship, I had the opportunity to work with different eCRFs, including ORACLE, MedidataRave, InForm and other less known. After data entry, queries

could be generated automatically or created by CRA, data manager or medical monitor. Queries resolution had to be answered within five working days. The queries generated automatically were addressed immediately. They were usually related to data entry errors. The other queries could be answered by me or, when required medical interpretation or expertise, by the investigator. I had also the opportunity to participate in the activities related to interim analysis and database lock. Before a database lock, all patients' data had to be recorded in eCRFs, all queries had to be answered and the validation of eCRF information had to be performed by investigators (eCRF investigators' signatures). These activities were usually performed against the clock.

In addition to eCRF completion, the upload of the required exams (X-rays, PETs, CAT scans, MRIs), procedures or neurologic scales (depending on the study) were also performed in the end of each visit in specific study platforms. These uploads were also my responsibility.

During the overall study conduct, investigators were alert for SAEs. When an SAE was identified, investigators asked for SC's help. I had the opportunity to report some SAEs related to oncology patients. These SAEs were immediately reported to the sponsor in 24h to 48h after its acknowledgement. In most of studies, this procedure was done in eCRF. It was also possible to report SAEs in a paper form filled by the investigator and sent by e-mail to the study safety team. Its queries were answered by the same system used to report the SAE (by e-mail or FAX when reported in a paper form or through the eCRF).

When a patient ended or discontinued the treatment, he/she had a study visit where the Investigator recorded the data required per protocol and evaluated the patient's status and next course of treatment (if applicable). I discontinued the patient in the IVRS/IWRS system, and the discontinuation reason was provided. The IVRS/IWRS discontinuation confirmation was archived in the Patient's File. The reasons for ending the treatment could be completion of treatment, progression of disease, unacceptable toxicity, AE, non-compliance to protocol, Investigator decision, pregnancy or withdrawal of consent. I participated in some end of treatment visits related to progression of disease (e.g. in lymphomas), completion of treatment (e.g. in breast cancer) and decision of the patient to end the treatment due to its long duration, and with the support of the Investigator (e.g. in multiple myeloma disease). When the patient ended the treatment, he/she began the follow-up phase in order to evaluate toxicity, progression of disease or survival status. These follow-up visits consisted in phone calls performed by study nurses or site visits performed by investigators. I was responsible for record the data of these visits in eCRFs.

e) Activities related to Monitoring Visits

Monitoring visits occurs after the site is initiated and continues until the site is close out. I had the opportunity to prepare and participate in many monitoring visits.

Before a monitoring visit, I prepared and organized all dossiers (Patient's File, Investigator's Site Files), to check if there was the need of archiving new documents or ask for updates of missing or inconsistent data between eCRFs and patients' health records. If so, I would note the aspects that needed the Investigator's amendment or clarification, so that the data could be updated before the monitoring visits. I would also verify if the eCRF was uptodate and answer open queries.

During these visits, CRAs verified the protection of patients' rights and well-being, the consistence between source documents and reported data in eCRFs and compliance with protocol and regulatory requirements.

In 2CA-Braga, monitoring visits were usually divided in three parts. First, CRA would review the pharmacy records related to IP accountability and would discuss the detected findings with study pharmacist. Then, investigator site files, patients' files and eCRF would be reviewed by CRAs and the detected findings (e.g. missing information or inconsistence information between source documents and eCRFs) would be discussed with me and, when necessary, with investigators. In the end of monitoring visits, CRAs would met with investigators to discuss the overall conduct of the study, including discussion of detected protocol deviations and strategies to avoid their occurrence in the future, review of study procedures (when needed), discussion of recruitment strategies (when needed), presentation of new information about the study (e.g. investigator brochures' amendments, protocol amendments, important safety information) and other important issues.

After a monitoring visit, I would met the action items identified by CRA and reported in a follow-up letter sent to research team.

2.2.2 Clinical Study Contract Negotiation Activities

Many parties may be involved in the conduct and management of a clinical study and it is important that each party has a clear reference of what is expected of them. Contract study agreement (CSA) should be in place prior to the initiation of any study and should be subject to periodic review to ensure that they remain uptodate and relevant. CSAs define specifically what will be done, to whom and when, and who will be responsible for costs. The content of a CSA typically includes the applicable regulatory requirements, the roles and responsibilities of each party, indemnification, insurance, subject injury, publication, intellectual property and confidentiality clauses. (23)

Indemnification means to compensate for loss or damage; to provide security for financial reimbursement to an individual in case of a specified loss incurred by the person. In the case of a clinical study, sponsor indemnification insures that clinical study participants and the institution are appropriately covered for losses resulting from their participation in the clinical study. This section of the contract is important because if the institution incurs in costs associated with subject participation these losses will be covered by sponsor.

The sponsor carries the majority of the risk and is therefore required to have adequate insurance as determined by regulatory requirements. Sponsors must carry a significant amount of insurance against subject's and institution's losses arising from participation in the clinical study.

If a research subject is injured during the course of a clinical trial, the sponsor has an obligation to cover expenses related to the injury if it was caused by the study; its practices, or products, such as the investigational drug or device. Accordingly, the subject's informed consent should reflect the protections to which the sponsor has agreed.

Scholarly publishing is a fundamental right and responsibility of researchers and institutions. Sponsors may review manuscripts prior to publication, but may not have final authority over approval. Publication clauses however typically grant the sponsor the ability to delay publication up to 30 days allowing for removal of confidential information as well as an additional 60 days for the filing of a patent application.

Intellectual property is property that results from original creative thought, as patents, copyright material and trademarks. During the course of a clinical trial the PI may either be the creator of intellectual property or a collaborator with the sponsor. The contract should set guidelines regarding inventions and who has ownership of them. The provision prevents the sponsor from gaining sole ownership of the investigators intellectual property.

Confidentiality is a set of rules that limits access or places restrictions on certain types of information. The contract should articulate each party's obligations of confidentiality and explain what information is considered confidential, the length of time that the information must remain confidential and how it may be used. (23,28)

During the internship in 2CA-Braga, I had the opportunity to participate in different clinical study contract negotiation processes related to interventional and observational studies. In 2CA-Braga, the negotiation process involved a dialogue between the sponsor (a pharmaceutical, biotech, or medical device company), the site (2CA-Braga) and the principal investigator until an agreement was reached on the terms of the contract.

The clinical study contract negotiation process usually lasted two to three weeks and was divided in four steps: review of the CSA draft, negotiations, finalization of CSA and release of the final CSA for signature. Upon receipt of the required documents (study synopsis and protocol), I reviewed the CSA draft to determine if it met all regulatory and institutional requirements. Then, I would draft the necessary revisions and submit them to the sponsor or sponsor's representative for review. The sponsor would accept some revisions and provided counter recommendations for others. This process continued as changes were suggested and then accepted or countered by each party until an agreement was reached. Once all parties had reached an agreement, the final version of the CSA was circulated for signature of the sponsor, PI and the president of 2CA-Braga Direction. The final contract signed by all relevant parties would be submitted to the ethics committee (CEIC for interventional trials and local ethic committee for observational studies) for approval. Once approved, the clinical study would begin.

Certain contract provisions have a significant impact on investigators and in the integrity of the institution. 2CA-Braga defined certain contract provisions as essential. I had to ensure their inclusion in the final contract study agreement. Subject insurance, indemnification and expenses reimbursement; medication supply after study conclusion (when applicable); research team constitution; payments timelines and distribution of the remaining value among research team are some examples of essential contract provisions, which needed to be included in the final CSA in accordance to 2CA-Braga politics.

2.2.3 "1as Jornadas de Investigação Clínica e Inovação"

Clinical research is a relatively new field in our country that has seen very rapid growth in the last few years. Availability of personnel appropriately trained to the specific requirements of the role they will perform in clinical research is critical for capacity expansion. The competitive advantage comes when the institution get people into a role and help them to know how to do that role well. With this in mind, 2CA-Braga organized the "1as Jornadas de Investigação Clínica e Inovação" (1st Clinical Investigation and Innovation Conference) on October 31, 2014. This event provided a space for education and training of clinical research professionals and to share ideas among different players of clinical research.

This scientific meeting was constituted by two workshops: "O(s) desafio(s) no início de um ensaio clínico" (The challenges in the beginning of a clinical trial) and "Como cumprir o protocolo num ensaio clínico" (How to comply with the protocol in a clinical trial). After these presentations, it was provided a space for discussion and sharing ideas during a roundtable moderated by Nuno Sousa

(MD, PhD), President of 2CA-Braga Direction. Synergy between industry and research and translational sites was the main topic of discussion. Paula Martins de Jesus (MD), Chief Scientific Officer of Novartis Farma; Eduardo Ribeiro (MD), Medical Director of AbbVie, and José Antunes (MD), Medical Director of Janssen participated in this discussion as speakers.

This scientific meeting was a very enriching experience due to the interesting input of different players related to translational research in academia and clinical research in Portugal. Speakers shared some strategies to investigators involved in translational research in academia and to investigators conducting studies of their own initiative to implement their studies with the support of pharmaceutical industry.

During this event, I provided support in a wide range of fields, including logistics and preparation of training material for each participant. The welcome registration desk was also my responsibility. These activities provided me the opportunity to improve my soft skills, such as organizational and management skills.

3. Discussion

Clinical research is a highly regulated and site-driven process that relies on a coordinated effort between the site, the sponsor, and all vendors providing study-specific services (as CROs). Sponsors contract the clinical sites to recruit subjects and CROs to ensure that clinical sites perform research as outlined by study protocols and record the data in an efficient and accurate method. (46)

My internship provided the opportunity to understand different players' perspectives and its main needs in clinical research.

As mentioned before, the first two months of my internship were performed in a full-service CRO: Eurotrials, Scientific Consultants. In this full service role, CROs like sponsors, are subject to heavy regulation by the federal government, must follow applicable state laws, must respect international guidelines, and are obliged to follow their own operating procedures. CROs are judged by the industry on the basis of the scope and quality of services provided, including the degree of adherence to the research protocol, regulatory requirements, and timelines; the quality of the professional working relationships with investigators and institutions, both academic and community-based; and the validity of the data. Further, CROs are subject to comprehensive audits by sponsoring companies, FDA, and other regulatory authorities. For all these reasons, CROs are being tasked with strict vigilance of all stages of the clinical trial process to ensure that the laws, regulations, and industry standards designed for the protection of human subjects and data integrity are maintained. (16,33,46)

During this period in Eurotrials, I participated in some qualifications and site initiation visits, as well as monitoring activities. These activities provided an overview of the tasks performed by a CRA/monitor and his/her "today´s" essential needs to meet regulatory and Sponsor requirements. Assess to source documents (like patient's health records, laboratory results, imaging results, among others) is the main issue identified. Usually, the patient's clinical data is recorded electronically and CRAs/monitors have no access to these source data. SCs print out these data and investigators validate the data by signing it. CRAs/monitors have only access to these printed data. They have no way to ensure that all clinical information about that patient is printed out and, consequently, that eCRFs are complete and accurate. It is necessary to implement politics and harmonized procedures in sites to provide a read-only view to CRAs/monitors only for health records about patients participating in clinical trials, ensuring the confidentiality of these data by signing a confidentiality disclosure agreement with site.

The other seven months of my internship occurred in a clinical academic research site: 2CA-Braga. Sites and investigators see clinical trials as a way to provide patient access to new healthy

technology, better patient's health monitoring practices and as an alternative financial source. However, there are some obstacles which difficult the research clinical activity. I identified some of these barriers.

One of these problems is that the research activity is perceived as add-on tasks, specially the assistance activity, for the majority of healthcare professionals. This results in a lack of motivation of the professionals because the clinical research requires a lot of time (it is necessary to register a lot of information about the patient, the patient requires a lot of care and a lot of administrative requirements). It is important to provide them the possibility of choosing the area of work: clinic, research or both. Time dedicate for clinical research is fundamental for more efficacy, dedication, motivation and positive results. It is important to support research teams, involve healthcare professionals in innovative projects, encourage, support and recognize the clinical research career as an important activity.

Other problem is the limited conditions to promote independent clinical research in Portugal. There are few investigators with fund, support, partnerships and enough qualified support structures to perform a clinical trial. It is important to review the legislation, in order to facilitate the sponsorship to investigators, for example by eliminating or decreasing taxes, reducing administrative complexity and costs and supporting the submission of clinical trials.

Other aspects include the fund provided by the State Budget for laboratories and research, clinical and non-clinical. In 2012, it was €74.5 million and in 2013 it was only €65 million. The review of fiscal incentives to clinical research is also very important as they may be seen as an investment incentive and may improve the competitiveness of Portugal. For instance, in UK, a National Institute for Health Research was created in order to manage funds to support investment. From 2012 to 2017, it approved a package of 102 million Pounds (≈ €142 million) for the development of 19 Clinical Research Facilities for Experimental Medicine.

It is necessary to recognize the strategic importance of clinical research for the improvement of healthcare and national economy. It is necessary to address these problems and invest in clinical research activity, and not exclusively in laboratorial and non-clinical research, to improve Portugal's competitiveness in clinical research area. (5,7,18)

Clinical trials are extremely demanding for any professional who works in clinical research area, including investigators, CTA/CRAs and study coordinators.

In Eurotrials, my internship consisted in a learning period, reviewing the academic background obtained during Pharmaceutical Medicine Master Degree and its application in "the real world of work", as well as learning about the company and its procedures. I really got enthusiastic with the

new environment and the tasks I observed from my colleagues in Clinical Trials Department, frequently contacting or visiting sponsors and sites.

In addition to that, I was responsible for the improvement of tools used by Eurotrials for site selection and qualification in future studies. This was accomplished through a database development based on previous feasibility questionnaires performed by Eurotrials and sponsors' feedback on them. The limited patient recruitment capacity and the lengthy bureaucratic processes were the main reasons for site exclusion, since these numbers did not achieve sponsors' expectations. As mentioned before, it is necessary to promote medical career through clinical research and reorganize clinical activity in order to increase the number of patients recruited. In Portugal the main source of recruitment is the own medical practice of the researcher and medical references from professional colleagues. However, there are many other sources that are not used in Portugal, because of the legislation restrictions, but are used in other countries like: referrals from clinical laboratories; mass media strategies (via newspaper or radio advertisements); mass mailings; blood banks (blood donors); local advertisements (notices on bulletin boards); or site specific databases. It is necessary to create funds and non-profit infrastructures for clinical research of investigator initiative. The CNPD role and the regulatory processes must also be reviewed and shortened to improve the competitiveness of Portugal. The creation of a dedicated regulatory body for clinical trial data related issues should be considered.

My improved skills of information management and organization were very important to the development of this database for future sites' selections and qualifications. During this first phase of my internship, I had the opportunity to participate in qualification visits, site initiation visits and monitoring visits which allowed me to understand the main common findings identified by CRAs/monitors. These activities were very important for my coordination activities in order to prevent and amend them with study teams before monitoring visits, and understand the main quality standards required by sponsors.

The second phase of my internship was mainly focused in study coordination and contract negotiation activities in 2CA-Braga. Working in a recent clinical academic center with three years of existence was a challenging opportunity. Despite its short existence, each professional had well defined roles and tasks. However, they worked as a team, supporting each other when needed. So, I felt part of the team since the beginning of my internship in 2CA-Braga and developed a close relationship with each member of the 2CA-Braga team.

The SC's day is never a routine. There are always new issues to address or follow-up, and many unforeseen issues and interruptions may occur. Scheduling appointments, preparing visits, eCRFs

data entry and queries resolution, protocol awareness, investigators meetings, qualification visits / site initiation visits / monitoring visits and contract negotiation activities constituted the daily-activities of my internship in 2CA-Braga. The need to coordinate among different tasks according to their priority resulted in the improvement of my organizational and management skills, as well as the capacity to solve problems and think critically. However, due to my inexperience in the beginning of my internship, most of these activities were supervised by the study coordinator manager. With increased experience and knowledge, I earned enough independence to do these tasks. This was an important milestone, since appreciation of my activities (both internally and externally) is very important to me.

The biggest challenge during my internship in 2CA-Braga was the fear of failure. Like in all jobs, all tasks performed have a consequence. However, in clinical research these consequences could affect the safety or well-being of a subject. Missing a procedure that collects information might seem like a minor deviation, but others, like a patient taking prohibited medication, are more serious. The pressure of these serious possibilities required my continuous attention for protocol details and constant protocol review to avoid protocol deviations and safety problems.

One of the things I enjoyed the most in clinical trials coordination activities was the opportunity to deal with different people involved in 2CA-Braga daily-activities: patients, investigators, study nurses, study pharmacists, other study coordinators, monitors and other sponsor's representatives. The real interaction with other people and, particularly with patients, instead of interact via e-mails, forms or phone contacts was very interesting and enriching. Participation in investigator meetings was also very appreciate, since these meetings provided an opportunity to interact and share ideas and experiences with other research team members developing the same studies in other "realities". The interaction with different professionals during my internship improved my communication skills, teamwork and my knowledge in clinical research area.

The entire internship was a learning experience, which provided the achievement of the majority of my internship objectives. Gain experience as a study coordinator was partially achieved, since I had no opportunity to participate in all phases of a clinical study. Participation in close out activities was not possible, since no study ended during my internship. However, all other objectives of my internship were successfully achieved.

The activities performed showed me how important it is for the sponsor to keep all relevant study documents and how everything sent to the sponsor must be identified in a standardized fashion and properly archived. The proper handling of study documentation and knowledge of study procedures and good practices are very important to a successful clinical study. My internship gave

me a practical overview of CRAs and study coordinators working environment and how these professionals are vital not only for the proper handling of study documentation, but also for the adequate performance of the trial, ensuring that the safety and rights of the patients are protected and that the study is carried out in accordance with the protocol and with all applicable regulatory and/or ethical requirements.

Embracing this experience was pretty challenging both personally and professionally. This experience showed me the importance of the different players involved in clinical research and the importance of their commitment for the improvement of public health.

A healthier society is a richer and more productive society!

4. Conclusion

Study coordinators and CRAs perform essential activities towards the successful execution of clinical research.

While the Principal Investigator is primarily responsible for the overall design, conduct, and management of the clinical trial, the study coordinator supports, facilitates and coordinates the daily clinical trial activities and plays a critical role in the conduct of the study. They are tasked with an expanding set of responsibilities including patient safety and recordkeeping, federal regulations compliance, ethics requirements compliance, interacting with Sponsors and Clinical Research Organizations and dealing with budget and contract negotiation.

CRA's main responsibility is to monitor clinical trials and work with study coordinators to ensure that all trial activity is in compliance with the protocol and ICH-GCP (Good Clinical Practice) guidelines.

Clinical Trials are increasingly complex. A recent report from the Tufts Center for the Study of Drug Development found the typical clinical trial requires about 170 procedures and has 13 endpoints. Additionally, the average study today has over 50 inclusion/exclusion criteria, over 180 pages of case report forms and 11 patient visits over 175 days. This has increased from the period 2000-2003 when there was an average of 105.9 procedures per protocol, 31 inclusion/exclusion criteria and an average of 55 pages of case report forms. (47)

Study coordinators are faced with increasing responsibilities while confronting trial complexity. It is critical for the protection of subjects and success of the trial that Study Coordinators are adequately trained to perform all of their delegated duties, and understand all of their responsibilities. CRAs are responsible for that training.

During my internship, I met most of my primary and secondary objectives. Collaboration as a CTA in a full-service CRO and as a study coordinator in a clinical research site provided me a perspective of the real standards and procedures involved in the implementation and management of a clinical study, which reinforce my background knowledge, both from BSc and MSc. In 2CA-Braga, the coordination of diverse clinical trials related with different therapeutic areas was very important to train a broad range of study coordination activities and also to strengthen my personal and soft skills. The coordination of these clinical trials and my collaboration with the Clinical Trials Department of Eurotrials provided me the opportunity to participate in qualification, site initiation and monitoring visits, as well as investigator meetings. Being part of 2CA-Braga team provided me a perspective of the working environment and an opportunity to participate in the communications' flow of clinical trials' approval processes in a clinical research site. However, participation in clinical

trials' submission processes to regulatory authorities was not possible. During my internship in Eurotrials there is no opportunity to collaborate with the start-up team of Regulatory Affairs Department, who is responsible for these activities. Conduction and preparation of audits and/or inspections, as well as participation in close-out visits was also not possible. There were no audits or inspections and none of my studies ended during my internship. Nevertheless, participation in contract negotiation activities was a very interesting opportunity, despite not having been identified as an initial objective.

Working in a CRO and in a clinical site was an exceptional growth experience for me. The work done was very focused on patient. Each day was an opportunity to provide an innovative treatment for a patient and improve their quality of life.

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